Pathology of Experimental Traumatic Abscess of the Brain

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In civil life, bacterial invasion of the brain resulting in the formation of an abscess, occurs relatively infrequently. Such lesions usually follow as a slow extension from a septic process in the neighborhood of the brain and only reach it after erosion of bone and the heavy connective tissues of the meninges. The development may involve weeks or years. It is fortunate that the central nervous system is so well protected from invasion, as the septic injuries of the brain are the most distressing wounds that a surgeon has to handle. During active warfare, on the other hand, the number of such casualties is enormously increased, and this study was begun with the hope of improving the treatment of these cases. Unfortunately, such a program has been but partially carried out and the work here presented represents the histologic control of the experimental traumatic abscesses of the brain.

The first part of the program undertook the study of the repair of aseptic wounds of the brain. This phase of the work was a repetition, on a limited number of animals, of the many similar experiments that have been carried on in other laboratories. Later a large number of animals (thirty-five) were subjected to varying types of infected injuries to discover, if possible, some of the general principles underlying the spread of infection and the factors governing the rate of spread. In every instance the dura was perforated; but the method or the details of infections were varied. Parts of the cortex were scooped out; perforations communicated with the lateral ventricle in some instances, while in others they only slightly injured the most superficial layers of the brain; foreign bodies of bone or metal were introduced into the wound; the skull was fractured in some instances along with the puncture of the central nervous system. In a word — attempts were directed toward reproduction of the wounds received at the battle front.

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It is important to recognize from the outset that an acute traumatic abscess differs in almost every respect from a lesion developing by slow extension. The rapid spread, with its fatal termination in a few days, as well as its healing by the formation of a connective tissue scar, presents an entirely different picture from the slowly growing process with a distinct tendency toward sequestration by forming a thick connective tissue capsule. The reasons for such differences are not to be sought in the kind of infection, the virulence of the organism, the kind of defensive mechanism employed by the affected part, or its anatomic position, but rather in the effect of the *injury* itself. Injuries involving the central nervous system at once cause a profound alteration in the normal circulatory and drainage mechanisms of the brain. The expression of such changes is swelling, or edema, and we have the beginning of a vicious circle, which takes but hours to be set in full motion. Long before anything which could be looked on as an adequate interference with bacterial growth has been instituted, the tissue is made more susceptible by anemia and edema. It is the surgeon's chief problem when operating on the slow eroding abscess of extension, to avoid exciting by trauma the phenomena of swelling and edema, and thus producing a rapidly fatal extension of the process.

The literature on brain abscess is clouded by the use of terms of which the exact meaning is not always clear. The susceptibility of the highly specialized nervous tissue to modifications of the vascular system, which might be inconsiderable in other parts of the body, opens up an easy field for softening and necrosis. It is to these processes that much attention was given in the older literature with efforts to establish their relation as fore-stadia to inflammation. These softenings were usually included under three heads — red, white, and yellow, according to the color seen at gross necropsy. The first two depend on the relative amounts of blood in the outer zone of the abscess; the more common red softening being the result of extravasated erythrocytes and vascular dilatation; while the white softening follows the anemic conditions and is more often associated with thrombosis of a vessel. The yellow, sometimes brown, softening is an older stage of the red softening and results from the breaking up of red cells into various oxidation products of hemoglobin.

The term "encephalitis" itself seems to be simple and straightforward enough, yet it suffers confusion with "inflammation," particularly within the central nervous system where vascular reactions are so greatly modified. It is repeatedly discussed in its relationship to red softening in a way that seems to cloud rather than clear the conceptions. The cause of the confusion is unquestionably attributable to the fact that our knowledge of the encephalitides is mainly classified after study of clinical history and resting very little on pathologic findings under the microscope. Our knowledge of the actions of toxins on the nervous system is very incomplete, but it is here that the key to many of our difficulties lies. The relation of abscess to encephalitis is described by Oppenheim,[1] as follows:

> Es gibt Encephalitiden, die mit dem Hirnabscess nichts zu thun haben, nicht in denselben übergehen. Es gibt ferner eine haemorrhagische Encephalitis, die sich mit einer suppurativen verbinden, respective in dieselbe übergehen kann (durch secundaere Infection). Dies gilt z. B., für die traumatische. Der Hirnabscess entsteht wahrscheinlich meistens in der Weise, dass von vorneherein zur Eiterbildung kommt; jedenfalls ist es nicht bewiesen, dass dem Stadium der Suppuration ein anderes voraus zu gehen braucht, in welchem das anatomische Bild sich mit dem der "rothen Erweichung" deckt.

The use of these terms has been purposely avoided in an attempt to introduce as little confusion as possible into this paper.

Experimental work on the central nervous system has been largely directed toward the simple repair of the brain lesions under aseptic conditions with a view toward establishing the part played by the various cellular elements — fixed and foreign — in the reestablishment of an equilibrium. The earliest researches were concerned with the ability of the nervous tissue to regenerate. The ganglion cells, for the most part, play a passive rôle and show but a feeble effort to replace destroyed elements. Their nuclei may show a preparation for mitotic division, but there is little evidence that this division is ever completed normally. The same holds true for the regeneration of the axone, within the central nervous system, when once the continuity of the latter is broken, nothing comparable to the replacement in a peripheral nerve ever occurs. The neuroglia cells are found to play a very important part both in inflammation and repair of the brain.

The best work on simple wounds of cortex was carried out in Ziegler's laboratory by Tschistowitsch.[2] To prevent the inflammatory factors from complicating the histologic picture of repair was his chief aim, and his choice of foreign body (small celloidin tubes kept sterile in alcohol) seems most fortunate, in that it produced practically no tissue reaction in the brain. He found that the nervous elements of the neighborhood made no attempt to reproduce the loss. The glia cells swelled up, divided actively — probably as a result of the change in nutrition. Tschistowitsch has no proof that they add to the host of phagocytic cells which digest and remove the destroyed tissue, but he does not conceive it impossible. He believes the phagocytic cells to be derived from connective tissue cells of the pia and from the adventitia of the penetrating vessels, partly from endothelial lining of blood vessels and leukocytes. The substitution of lost parts is made almost entirely by connective tissue. Within a few days the young fibroblasts derived from the pia mater may be seen wandering into the wound edges with their long axes parallel to the axis of the lesion. Side by side grow new vessels. The connective tissue growth was much less in wounds produced by introduction of celloidin tubes. The glia takes no part in the formation of the cicatrix which replaces the destroyed elements, but merely confines itself to the elaboration of a secondary zone of sclerosis around the scar. The sclerosis varies in amount with the duration of the original stimulus.

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[1] Oppenheim, H.: Die Encephalitis und der Hirnabscess, Nothnagel's Specielle Pathologie u. Therapie, Wien. **9**: 1903.

[2] Tschistowitsch, Th.: Ueber die Heilung aseptischer traumatischer Gehirnverletzungen, Ziegler's Beiträge **23**:321 (2 plates), 1898.

The activity of the neuroglia in inflammation as well as in normal conditions has been elaborated on by Alzheimer.[3] He postulates two kinds of neuroglia cells, indistinguishable from one another, which exist as a normal supporting reticulum. Those of the first type are essentially part of the fibrillar network and they are solely occupied with the maintenance of this network. A second variety may easily free themselves and become ameboid. This group, under the stress of great degenerative processes, takes on special forms, assimilates degenerated products, and carries them to the perivascular spaces. Thus they may contribute to the large phagocytic mononuclears seen in close association with the brain abscesses.

RELATION OF MACROPHAGE TO ABSCESS

The most striking characteristic of destruction of the nervous tissue is the appearance of these large mononuclears. In 1841, Gluge[4] called attention to *Körnchenkugeln* as a diagnostic point in inflammations of the central nervous system. These were collections of *Körnchenzellen,* about which all subsequent discussions concerning inflammatory processes in the brains revolved for the following half century. Virchow[5] described an "encephalitis neonatorum" in which he regarded the *Körnchenzellen* as a product of a fatty metamorphosis of neuroglia cells. Hayem[6] looked over twelve supposedly normal new-born brains and found granular cells (*Körnchenzellen*) which he took to be the normal appearance at that period of growth. In 1871, Jastrowitz[7] demonstrated their presence in children's brains unquestionably normal because they were dead only as a result of accident at birth. In addition he proved that there was an apparent irregularity of distribution. He noted the greater number of these cells to occur in these areas where fibers were developing more rapidly than in other regions of the brain — "besonders stürmischen Entwicklungstypus." He thought them of glial origin. Boll[8] identified them in normal chick embryos at from twenty to twenty-one days of incubation, and found them extremely ameboid on the warm stage. He believed that they brought fat for the deposition of myelin on the axis cylinder. Flechsig[9] completely correlated their distribution with the time of myelinization of the fiber tracts, yet he was unwilling to commit himself as to their origin, but inclined toward a view that they were glial. The microchemical work of Wlassak[10] solved the discrepancies which gave rise to so many diverse interpretations. On the one hand, the followers of Virchow regarded these granular cells as degenerative in character and consequently to be viewed as pathognomonic of inflammation. On the other hand, Jastrowitz and his followers believed their occurrence was a normal physiologic event, especially when associated with early development. Chemical analysis proved both of their views correct although the controversy had lasted for many years. Granules in cells, then, could be lecithin, protagon, albumin, decomposition products of hemoglobin, fat, and so on. With this conception, the cells previously grouped as "Körnchenzellen" have been variously subdivided, according to the conception of the author as to origin, morphology, or physiologic activity. The more recent literature has become more and more interested in the function and activities of cells and less with exact morphology. Such interpretations are open to the possibilities of greater mistakes, but also allow a more intelligent effort toward control of cellular reactions in inflammation and repair.

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[3] Alzheimer, Alois: Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu dem Abbauvorgängen im Nervengewebe, Histol. u. Histopathol. Arb. über Grosshirnrinde (Nissl), Jena **3**: 1910.

[4] Gluge, G.: Experimente über Encephalitis, Abhandlung z. Physiol. u. Path. No. 2, Jena, 1841, p. 13.

[5] Virchow, R.: Kongenitale Encephalitis und Myelitis, Virchow's Arch. **38**:129, 1867.

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[6] Hayem, G.: Etudes sur les diverses formes d'encefalite, Paris, 1868.

[7] Jastrowitz, M.: Encephalitis und Myelitis des ersten Kindesalters, Arch. f. Psychiat. **2**:389, 1870; **3**:162, 1872.

[8] Boll, Fr.: Die Histologie und die Histiogenese der nervösen Zentralorgane, Arch. f. Psychiat. **4**:1, 1874.

[9] Flechsig, P.: Die Leitungsbahnen im Gehirn und Ruckenmark des Menschen, Leipzig, 1876.

[10] Wlassak, W.: Die Herkunft des Myelins, Arch. f. Entwicklungsmechanik **6**:453, 1898.

Among the writers of the last decade are found Nissl[11] and Mertzbacher[12] who have attempted to read activity into the processes of destruction and repair, each from slightly different points of view. The experimental work of Nissl has served to emphasize the "Gitterzell" as a pure and simple phagocyte whose chief rôle is the restoration of order after a destructive process has set in. The granular cells should no longer be looked on as a specific element in inflammation, for they are quite often the cells wholly concerned with reparative process. They appear in every situation where necrotic tissue-masses (foreign bodies) must be removed. If one chances on these cells at some distance from the lesion within the perivascular spaces, more than likely they have come from the focus of infection, laden with waste products and are making their way into the channels of tissue-drainage.

Mertzbacher wishes to reclassify these cells seen in inflammation into a physiologic group and ignore their origin entirely. His term "Abräumzell" suggests a purposeful activity and includes both "Aufbauzell" and "Abbauzell." In this sense it is better than the physiologic term "Macrophage," but the latter is probably doomed to stay because of its priority. The term "Macrophage," proposed by Metschnikoff, refers only to the power of the cells to phagocytize large elements. The functional division made by Mertzbacher was between physiologic and pathologic cells — the normal physiologic "Körnchenzell" of the embryonic central nervous system (clearly an "Aufbauzell") belongs to the group of cells known as "Abräumzell of the adult.

Friedmann[13] published many papers on his experiments on encephalitis, emphasizing the importance of the epithelioid cells. His conceptions and observations seem in no way to have contributed to the solution of the problem.

THE WALLING-OFF PROCESS

The question of greatest interest to the surgeon has always been the walling-off process. Where the invasion is slow, the fibroblasts lay down a very efficient barrier of connective tissue ahead of the infection. The time necessary to bring about the protective barrier has been variously estimated, and the lower limits necessary for its formation have been the subject of much discussion. The knowledge gained from aseptic wounds helps us but little. There the young fibroblasts may be seen on the fifth to sixth day, taking active part in the repair, but in no sense can they be looked on as capable of resisting the spread of an infection. The differences of opinion are largely the results of inability to absolutely demonstrate true connective tissue fibrils. Preceding the actual fibril formation, a collagenous material is laid down, and this takes a progressively deeper stain, similar in character to the finished connective tissue.

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[11] Nissl, F.: Zur Histopathologie der paralytischen Rindenerkrankung, Histol. u. Histopathol. Arb. über Grosshirnrinde **1**:315, Jena, 1904.

[12] Mertzbacher, L.: Untersuchungen über die Morphologie und Biologie der Abräumzellen im Zentralnervensystem, Histol. u. Histopathol. Arb. über Grosshirnrinde (Nissl) **3**:1, Jena (7 plates), 1909.

[13] Friedmann, M.: Encephalitis und Hirnabscess, Handbuch der Pathol. Anat. des Nervensystems (Flatau-Jacobsohn) Berlin **1**:494, 1904.

This process of repair in a sterile wound is in no way comparable to the formation of a protective wall in an abscess. The latter forms in the intermediary zone between the living and dead tissues, attacked on one side by the toxins and supported on the other by a very much impaired circulation. The fluids bathing the young fibroblasts which wander very early into the outer zone of the abscess are certainly very different from those present in a sterile destruction. It is generally conceded that an adequate connective tissue barrier forms very slowly. Observers have made various estimates from clinical history, namely, Lebert, from 3 to 4 weeks; Schott, from 7 to 8 weeks; R. Meyer, 7 weeks; Gull, 10 weeks; Huguenin, 53 days a thin membrane, 83 days a thick resistant wall.

The lowest estimate in these figures shows the utter hopelessness of waiting for such a fibrous barrier to help us in treating a traumatic infection of the central nervous system. Furthermore, it must be remembered that, were its formation possible, it would be of doubtful value when one considers that the completely encapsulated process slowly encroaches on the healthy tissue owing to toxic products seeping through the capsule, through pressure, or through vascular changes. It may be repeated that the traumatic abscess is something different from the encapsulated variety and by careless handling the latter may be transformed into the former. The infection in the brain spreads so rapidly after an injury that there is no time for the interposition of a connective tissue barrier, and a rational treatment can never hope to receive aid from such a slow and really ineffectual mechanism.

METHODS EMPLOYED IN EXPERIMENTAL PRODUCTION OF TRAUMATIC ABSCESSES

It was early discovered that an abscess in the brain of a cat developed with great uncertainty unless a positive—what might even be called a massive dose of bacteria was introduced into the wound. Simple puncture wounds often healed *per primam* although no efforts were made to sterilize the instruments or tract. An animal's resistance to infection, even after rupture of the dura, was found to be quite remarkable. There seemed to be little tendency for organisms to grow down into the brain from the skin, or for the few carried in with the instruments, to gain a foothold. In order to inaugurate an infection, an injection of from 0.1 to 0.3 c.c. of bouillon culture or pus in varying dilutions was made into a wound. The ordinary pyogenic organisms cultured from human infections were found to be very feeble in virulence. Pure cultures of bacteria obtained from abscesses in cats proved to be more efficacious. The most rapidly fatal lesions were produced by taking pus from a cortical abscess of one cat and injecting it directly into the brain of another. Some of the animals treated in this way survived less than twenty-four hours. Not uncommonly a spread along the whole track of the wound instituted a cellulitis within the scalp. Such secondary complications were treated by evacuation as soon as they developed, but at times the subcutaneous infection would spread over the entire head and as far forward as the eyes. The cats within this series were not all normal when the experiments were started, often having been used for other observations on the central nervous system. Such a past history often changed the course of the abscess as well as the cellular reaction of the host.

A nail of given length was sharpened for making perforating brain injuries and a known weight was put behind it; this was then allowed to fall a definite height. The method was quickly abandoned because of the uncertainty of getting a standard wound. The principal difficulty lay in the rotundity of the cranium. Blows administered in this manner tended to be deflected so that considerable subcutaneous trauma might be inflicted without perforating the skull. In one experiment a piece of infected copper wire was forced into the brain substance through the nail hole. Another method employed was to remove a cylinder of the skin, skull, dura and brain, and to place infected foreign bodies in the defect. Such a procedure at times reached the lateral ventricle, more often the infection did not start within the ventricular system. A trephine was used for the skull and a cork borer to remove soft parts.

The greater number of experiments were so made that there was no room for expansion of the brain. A bluntly sharpened instrument, 1 mm. in diameter and provided with a shoulder so that it could only be inserted to a depth of 6 mm. from the surface of the skin, was used to make an opening for a hypodermic needle. Such wounds caused little or no trauma to the subcutaneous tissues and were just sufficient to penetrate the outer zones of the cortex. Rarely this struck a sulcus and the syringe needle actually ended in the subarachnoid space without penetrating the cortex. At necropsy such failures were indicated by a purulent meningitis without involvement of the brain. The quantity of diluted pus or bouillon culture used was sufficient to cause a localized rupture of the tissues accompanied by slight hemorrhage. In every case an initial spread of the injection mass into the subarachnoid spaces was unavoidable.

A few attempts were made to completely localize the infection to the point of inoculation by injecting the septic material into the exposed cortex through a trephine hole and immediately sterilizing the surface. The results of such a procedure were very disappointing as they were just as susceptible to a meningeal spread as were animals treated similarly without sterilization. Attempts were made to cure the experimental abscesses either by trephining and draining, or by trephining and irrigation. The number of attempts was so small that no conclusions could be drawn. Actually, the number of spontaneous cures was greater than the number following attempted therapy.

CLINICAL HISTORY

Little importance can be attached to this part of the work in animals. Often, when the virulence of the infecting agent was low, the animal behaved as if normal for a day or two. On the other hand, with more virulent strains injected with pus, the protocols show that the cats were sick immediately after the experimental injection. Following concussion or cortical ablation the animals were dazed or showed little desire to move or eat; at such times there was a definite weakness in the hind legs but no actual paralysis. After considerable trauma they might be unable to walk or crawl, but these reactions should not be considered in any differential diagnosis concerning the type of lesion. The history of the present illness would be enough to account for the reaction. No attempt was made to record temperatures as there is so much variation under the condition of experimentation. After simple perforation the element of trauma was minimal, and the record of "quiet" or "less active than normal" would be the only signs of disturbance. The discharge of pus from the wound gave absolutely no clue as to the process developing within the cortex. As a matter of fact, this hole in the bone was very quickly sealed by granulation tissue and the subcutaneous reactions had no effect on the cortical infection. Very few of the cats were sacrificed but were allowed to die spontaneously. The animals included in the end of the series were often found dead in less than twenty-four hours after inoculation.

PREPARATION OF MATERIAL

The animals were embalmed as soon as possible after death by injection of 10 per cent. formalin through the aorta. A block including the skull and cervical vertebrae was then suspended in the same fluid until ready for study. The relations of the meninges to the bone were studied and gross macroscopic descriptions were recorded and the tissues were embedded in celloidin. Hematoxylin and eosin, toluidin blue, Van Gieson, and Mallory's connective tissue stain were applied to the sections. It is evident that such technic precludes a study of the finer cellular changes in the nervous system, but it preserves the intracranial topography and does not interfere with observations of the cellular reactions.

MACROSCOPIC APPEARANCE OF BRAIN ABSCESSES

The central nervous system, as usually seen at necropsy, gives little exact knowledge of the relations obtaining at the time of death. Dislocations and changes in shape due to pressure are largely lost when the soft brain is taken from the skull. By injecting formalin into the aorta at death and fixing thoroughly by immersion, all of the gross form relations are preserved. The changes in the size, shape and position of the ventricles are maintained faithfully and any distention of the leptomeninges by fluid-accumulations is undisturbed. Unless such fluid in the subarachnoid space is coagulated by fixation, its appearances of distention are largely lost if the meninges are not hardened in situ.

The most striking change produced by these traumatic abscesses was the increased tenseness of the brain. This showed itself most markedly by a herniation of the subjacent nervous tissue through a defect in the dura and skull. Whole gyri were capable of slipping out when the hole was large enough, taking with them a fairly intact blood supply. Such protrusions rapidly underwent necrosis in the central portions and were sloughed off. The most rapid expulsion of nervous tissue followed the simultaneous development of a subdural abscess away from the dural defect, and this greatly added to the fungus which developed as a result of increase in size of the brain itself. Palpation of such a brain revealed an unusual tenseness, and any splitting of the dura due to careless removal allowed the brain to bulge out. The evidence of swelling might extend down the cord where the markings of the intervertebral spaces could be seen in outline. On the dorsal surface of the cord these segmental corrugations were often great enough to be felt by running the fingers up and down the unopened dura. The result of the swelling was to partially obliterate the sulci of the brain so that they appeared as mere lines when viewed through the dura. Such conditions might still exist at the end of a week. The effects of swelling were usually more marked on the affected side, but they might involve both cerebral hemispheres equally. The macroscopic evidences of meningeal infection, hyperemia and petechiae, clouding of the normal markings and heavy purulent exudate, showed considerable variation. In six of the experiments, no evidences of an inflammation spreading beyond the point of injury could be demonstrated macroscopically. In seven instances, there was a progressive advance of the process over the injured hemisphere with the formation of a heavy purulent exudate which completely obliterated the brain markings on the affected side. There was a distinct tendency to stop at the midline along the falx cerebri (Fig. 5), and to spare the temporal pole and the occipital lobe. Another peculiarity of distribution, in two experiments, was a normal looking cerebrum surrounding the injury with no macroscopic evidences of meningitis over the brain; the cord, medulla and cerebellum, on the other hand, were totally obscured by a thick layer of yellowish exudate. In these instances either by direct injection into, or subsequent invasion of the lateral ventricle, the ventricular system became the pathway for an extension of the infection to the natural outlets to the subarachnoid space — the foramina of Magendie and Luschka. At these points the process attacked the meninges spreading over the hind brain and down the cord. In fifteen of the thirty-five animals, a generalized meningitis was present at death. Where only a small opening existed in the skull and there was no chance for the nervous tissue to herniate, the defect was filled with a plug of coagulated debris which quickly began to organize. Some of the injuries were very close to the mid-line and an opening was made into the large vein emptying into the sagittal sinus. This was followed by a hemorrhage which almost completely covered the cerebral hemisphere, extending to the base of the brain and out along the rhinencephalon.

On section, the gross specimen showed remarkable changes in brain-bulk, which brought about extensive dislocation of the entire brain, especially where the lesion developed rapidly within the normal confines of the skull. The affected hemisphere might occupy one-third again as much space as the unaffected one, enlarging at the expense of the latter (Fig. 10). This encroachment of the injured side was greatest at a point midway between the vault and the base of the skull. At these fixed points the nervous tissue was anchored by the meningeal vessels, and had no opportunity to be displaced. The result of this was a curved midline with the convexity looking toward the unaffected side. The transverse section through the lesion showed the greatest changes, but the entire affected hemisphere might bulge beyond the normal limits (Figs. 10, 11). As long as the brain herniated, as in a decompression (Fig. 19), the normal appearance of the mid-line was unaffected. Here the local increase of brain-bulk took the line of least resistance and instead of compressing healthy brain tissue, release was afforded by protrusion from the skull.

Another effect of increase in size of the brain was the encroachment on the spaces ordinarily filled with cerebrospinal fluid. Such a condition arose in most of the experiments included in this series, because the abscesses developed within the intact skull. The gyri were forced together and the normal subarachnoid tissue between them was compressed until it appeared as a mere linear slit. The normal, rounded gyrus was flattened out against the dura and the contour approached a straight line with the sulci meeting it at right angles. It is conspicuously shown in Figures 11, 16 and 18. The reactions of the ventricular system were very definite. They were complicated by infection in eighteen instances, of which three were unquestionably inoculated at the very beginning of the experiment, whereas fifteen were infected by extension of the process into it. Whether invaded or not, there was present, in nearly all of the experiments, a tendency toward the production of a slight grade of hydrocephalus (Figs. 8, 10 and 11). If the ventricle was perforated by the original injury, the entire ventricular system rapidly dilated with pus (Fig. 18) forming a pyocephalus of moderate grade. Where the original abscess eroded its way into the ventricle, the latter was soon filled with a purulent exudate on the affected side. The contralateral ventricle was likewise distended, but as a rule the character of the exudate was clear and coagulated with fixation (Fig. 10). The entire ventricular system may be thus dilated. No interference to the normal outflow of cerebrospinal fluid could be discovered at the foramina of the fourth ventricle. An abscess developing within a confined space compressed the lateral ventricle directly beneath; if the brain was able to herniate from the skull, the ipsilateral ventricle was distended at that point. On the whole, the contralateral ventricle is more widely distended than the ipsilateral.

The bacterial invasion of the brain substance has shown marked variations in the rapidity of its spread, but an almost universal predilection to follow the fiber tracts rather than spread in the cortical gray matter. The result of such a mode of spread was the production of a pear-shaped lesion (in the early stages), the narrow neck of the abscess being located at the point of destruction of the cortex. At times this extended around neighboring sulci by picking out the fibers and from there it more slowly eroded its way through the cortex to the meninges. In some of the most virulent infections an abscess 2 cm. in diameter was found within twenty-four hours, being large and toxic enough to kill the animal. The core of the abscess quickly became granular and opaque. This necrotic center was surrounded by a more translucent gray zone while the latter, in turn, was hemmed in by a zone of punctate hemorrhages. The tendency toward ecchymosis was absent in very few instances, but often extended for a considerable distance beyond the actual necrotic process. By carefully picking (with a delicate instrument) the edges of the process it was impossible to demonstrate a wall of any tougher consistence than the normal nervous tissue itself; the edges everywhere were quite friable.

The central core was usually granular and somewhat inspissated, but in some instances it was represented by a clear gelatinous exudate (Fig. 12) which projected slightly from the plane of section. The walls of such a cavity were smooth. In one experiment there was present a gas-forming organism which produced a considerable gas filled cavity in the center of the abscess. As a rule, however, the abscess consisted of a necrotic core located for the most part in the white matter of the cerebrum and surrounded by a zone of small ecchymoses.

Marked change in color took place in the macroscopic appearance of the fiber tracts. It appeared first as a more translucent core developing within the center of the fiber tract near the abscess and radiating for some distance on the affected side. In the affected area, a thin fringe of white matter adjacent to the cortical gray preserved its pearly white appearance and served to set off the central part by contrast (Fig. 8). In most of the experiments this change was fairly well limited to the affected side, but occasionally it extended into the opposite hemisphere along the corpus callosum. Gradually this gray translucence spread to the outer limits of the fiber tract and the distinction between gray and white became almost obliterated (Fig. 12). It seemed to bear some relation to the pressure, inasmuch as it was less well developed in those cases in which a decompression had allowed the brain to expand.

There was a marked tendency for the arachnoid to be split away from the dura by a rapidly developing meningeal abscess. Even though a hole exists in the skull (Fig. 19), this collection of pus cannot evacuate itself because the expanding nervous tissue forms an efficient plug for the outlet. In twelve instances a considerable collection of subdural pus was present. A meningeal abscess of remarkable size followed an attempt at osteoplastic repair of the skull after the cortical abscess had been completely healed (Fig. 8). Such a meningeal abscess developed with remarkable rapidity and at times invaded the opposite hemisphere by extending down one side of the falx and back up the other. These abscesses have shown no tendency to invade the cortex, although they must exert a considerable pressure upon it.

MICROSCOPIC APPEARANCE OF BRAIN ABSCESSES

Under the low power of the microscope, the typical brain abscess in these experiments presented three well marked zones — a central core of necrosis, a surrounding fringe of leukocytes and a zone of vascular engorgement and hemorrhage. In the first two, all semblance to structural characteristics common to the tissue was obliterated, while the last, called by many writers "the necrobiotic zone," still maintained characteristic appearances and staining reactions, and represented the transition between the dead and the normal living tissue. The destroyed center took the eosin stain very poorly and the hematoxylin not at all, except for patches of dense blue colonies of bacteria. The densely staining bacterial masses were found to be thickest in the periphery of the necrotic zone, just inside the cellular layer. Often within the necrotic zone surrounding a blood vessel, appeared small islands of tissue which had not been totally reduced to a homogeneous appearance. The "burnt-out" character of the central core may be extensively developed within a few hours if the virulence of the organism is great. Where the process developed more slowly, the abscess had a laminated appearance (Fig. 14), as the cellular zone progressively died and was in turn encircled by a new layer of exudative cells. The width of the second or middle zone varied considerably. In a rapidly advancing process this layer was well developed and the cells infiltrated the tissues in enormous numbers. At such a time the outer limiting edge was comparatively smooth (Fig. 13). Apparently, the resistance of the tissue to invasion showed little local variation, and the process swept through the brain without the usual degenerative changes occurring in front of it. Beyond the leukocytic zone, as seen under the low magnification, there were changes referable especially to the vascular system. Red blood corpuscles had extravasated in quantities sufficient to obscure the texture of the nervous tissue. Serous infiltration may give it a loose watery appearance. Radiating from the abscess, the perivascular spaces were often packed with nucleated cells for a considerable distance (Fig. 3).

Low magnification demonstrated most clearly the relative resistance of the different regions of the cerebrum to infection. The fiber-tracts were involved more rapidly and extensively than the gray matter. The cortical gray itself showed differences in the susceptibility toward destructive processes. Thus the molecular zone might survive, although for a considerable distance (Fig. 16), the ganglionic layers beneath and the meninges above showed complete destruction. Beyond the outer zone of hemorrhage and vascular change, the fiber tracts are usually much lighter in density of eosin stain than normal fibers. The initial stages of the translucent gray appearance, developing in the fiber tracts concomitantly with the increase in intracranial pressure, could be made out only under very low power of the microscope. This change was manifested by a slightly lighter stain with eosin when compared with the normal fiber bundles of the unaffected hemisphere. Under the high powers the differentiation between the affected and unaffected sides was impossible until the process had progressed for a considerable period. The subdural location of the meningeal abscess is well brought out in Figure 14. Owing to the shrinkage in embedding, an artificial separation has been produced between the abscess and the pia-arachnoid. The latter was heavily infiltrated with cells, but was distended very little more than normal.

A minute study of the central necrotic zone, during the early stages, revealed the shadows of exudative cells, faintly staining with eosin.

Rarely was it possible to recognize any of the original structures excepting the larger blood vessels. By crushing bits of this necrotic center on a slide and staining it with weak aqueous methylene blue, a very good idea of the composition of the mass could be gained. It was there easy to pick out the structural elements, ganglion cells, glia cells, polymorphonuclear and mononuclear leukocytes making up the dead core. Almost every cell contained organisms, and it was striking that the bacteria were for the most part intracellular. At times the cells and their contents took no stain whatsoever, appearing as a simple envelop with refractile inclusions. Again, the cellular envelop contained from ten to twenty stained organisms, but otherwise was colorless. Still other cells have been found in which the blue-stained nucleus could be made out in addition to the bacteria. The intracellular position of the organisms could not be seen in the cleared and stained sections, partly as a result of the thickness of the sections, with a resultant superposition of elements, and partly because the clearing made cell boundaries undistinguishable.

The distribution of organisms within the necrotic center was fairly uniform, but as one neared the zone of cellular exudate the number and density were greatly increased so as to form a bluish zone inside the border of living cells. Figures 7 and 15 show very clearly these bacterial masses flourishing on the very rim of the necrosis. In Figure 15 one gets the impression of an actual radial advance of these masses into the leukocytic zone and a trail of destruction in their wake. The organisms were usually mixed where pus had been the original infecting agent, but most frequently in these experiments the destructive organism was a streptococcus. This was the organism which was found massed behind the leukocytic zone. The isolated islands appearing within the necrotic area were built around the larger blood vessels and were composed of collections of exudative cells or at times mainly red blood corpuscles in a fairly good state of preservation.

The "burned-out" appearance was rather extensively spread when the lesion developed rapidly and then could be seen the pale shadows of the exudate over wide areas. In a short time this was replaced by an amorphous granular detritus in which a few bacteria could still be seen. The liquefaction of the debris was a rather rare phenomenon, only occurring in two instances. The failure to find this more frequently might be referred to short period of survival of the animals in most of the experiments. Here it was not unlikely that the liquid was a coagulated exudate of a fluid free from cells. Microscopically, such an area appeared perfectly homogeneous, eosin-staining, and with no indication of any formed elements or bits of debris.

Surrounding the necrotic core was a zone of cells which was made up of a preponderance of polymorphonuclear leukocytes in the early stages. Very rarely the mononuclear infiltrating cells outnumbered them; then no accountable reason could be found. These small cells were the derivatives of the circulating blood and formed a closely packed boundary to the abscess. The outer limits of this zone was usually beyond the extension of demonstrable bacteria, sometimes, however, it was coincident with their growth, and very rarely the bacteria spread beyond their outer limits into tissue, recognizable structurally as nervous tissue. Sometimes, in localized areas, the bacteria grew beyond the infiltrated zone into the perivascular sheaths with no cellular reaction (Fig. 13). The more usual conditions are illustrated in Figures 7 and 15, where the leukocytes interpose themselves between the bacteria and the surrounding nervous tissue.

Enveloping the entire process was a shell of tissue in which the vascular changes were the predominant features. All the vessels were engorged with red blood cells, which in many places have escaped into the tissues. The ground-work was also infiltrated with a serous exudate, often coagulated and containing spicules of fibrin. There were many isolated leukocytes scattered in this area, but in general they were found in greatest numbers in the perivascular spaces (Robin) radiating from the edges of the abscess. Often the smaller vascular branches were so densely surrounded by these wandering cells that the lumen appeared compressed (Fig. 3). At some distance from the lesion they were confined absolutely to the perivascular spaces, but, as the edge of the leukocytic zone was approached, they invaded the tissue in increasingly greater numbers. The distention of the tissue elements by exudate was quickly followed by swelling up of the glia cells. These are normally inconspicuous with little protoplasm about the nucleus; in these cerebral infections after a few days they appeared more rounded and at times in the process of division by mitosis. The most striking phenomenon was the escape of erythrocytes from the vessels; this happened in varying degree in all of the experimental abscesses in this series. At times the ecchymosis was great enough to form an almost unbroken ring of free erythrocytes around the zone of exudative cells (Fig. 6) even extending for a considerable distance into what might be viewed as otherwise normal tissue. At other times they appeared as small punctate hemorrhages scattered around the periphery of the lesion. Such collections of red blood cells usually formed a locus of increased resistance toward bacterial involvement. These islands of red cells indented the advancing edge of the process (Fig. 7) and only succumbed after being entirely surrounded by the infection. The ganglion cells in this outer zone showed the classic signs of degeneration — clumping of the Nissl bodies, chromatolysis, shrinking of the nucleus and disappearance of the cell. After several days this zone was invaded by young fibroblasts, most of which were derivatives of the pia-arachnoid and of the adventitia of the neighboring blood vessels. Elongated typical cells could be found developing from the meninges at the edges of the wound, and from this point they extended into the depths within the zone of necrobiosis. The adventitial sheath of the blood vessels in the neighborhood of the lesion also proliferated by mitosis and furnished fibroblasts which extended into the outer limits of the abscess. In none of the specimens was there the slightest evidence of an orderly arrangement such as might be looked on as a foundation for a capsule — nothing which could be interpreted as an early attempt on the part of the fibroblasts to interpose a barrier against the spread of the infection.

For the first two days in the development of the abscess, the infiltrating cells were composed almost entirely of leukocytes. After that the necrobiotic zone was invaded by increasing numbers of large mononuclears, known as "macrophages," which collect where the extravasation of blood is greatest and among the fiber tracts that were undergoing secondary degeneration. These cells were most conspicuous for their size, actively engulfing the products of tissue destruction until they reached enormous proportions. Such cells are so well known that an exact description of their appearance is superfluous. At times they were gathered in close formation occupying entire microscopic fields, their pale reticulated bodies and eccentric nuclei being in close apposition to one another. The activities of these cells in removing a blood clot are truly remarkable. This is well illustrated in Figure 16, a photograph of a brain section into which a button of bone was forced and a dense blood clot resulted. The lower central portion of the mass has been almost entirely removed by activity of these cells. Most of these are derived from the pia-arachnoid, adventitia of blood vessels, endothelium and neuroglia cells, where they could be seen to develop from the fixed tissue cells and to take on the characteristic lattice-work structure, typical of the protoplasm of the macrophage. When found among the degenerating fiber tracts their bodies were loaded with droplets that stained with osmic acid. At times they formed an almost unbroken ring around the abscess just outside of the leukocytic zone. As the process spread they were included within the middle zone, but one gathered the impression that they were not associated with the active process in the same way that the exudative cells of the blood were concerned. Rarely these large phagocytes had entered the outer zone of the abscess in considerable numbers within forty-eight hours. Some of these animals had been previously used in other experiments and, in all probability, a considerable number of the macrophages were in the meninges at the time of the production of the abscess.

The traumatic brain abscess has been found to be occasionally accompanied by a considerable amount of transudate extending throughout the lesion. The zonular arrangement just described was then more or less obliterated. The pattern became a sort of mosaic of dead tissues, islands of exudative cells, homogeneous patches of eosin-staining material, and masses of red blood corpuscles. Throughout were crystals of fibrin embedded in a clear matrix, or woven among a loose collection of leukocytes. In these instances the actual number of organisms seemed to be very much reduced as compared with those in which a well formed necrotic center was produced.

The ganglionic layer and fiber tracts in the immediate neighborhood just beyond the outer zone of necrobiosis showed the well known signs of degeneration. The nerve cells whose fibers were involved swelled up and slowly degenerated. The neuroglia cells became much more prominent and showed mitotic figures. Their normally inconspicuous cell body increased in size, the appearance of the protoplasm became more watery and their processes, thick and rounded up. Their nuclei were often increased in number. The nerve fibers, undergoing secondary degeneration at a distance from the actual lesion, showed swelling of the axis cylinder, which broke up into granules of bizarre shape. These collected into a network with a more or less even mesh. Later they were invaded and removed by the large phagocytes. The most remarkable phenomenon about the spread of the abscess was the resistance to destruction shown by the molecular zone — quite frequently the ganglion cells beneath were destroyed completely for a considerable extent and it was possible to identify this thin strip of nervous tissue embedded in a mass of leukocytes and bacteria.

SPREAD OF INFECTION INTO MENINGES

The meninges in the neighborhood of the lesion were quickly infiltrated with leukocytes which formed a fair degree of protection against a rapid spread of the infection in the subarachnoid space.

Where a decompression allowed the brain to herniate, compression of this space apparently favored the effectual shutting out of a generalized spread, but this factor was never demonstrated. A common complication was the separation of dura and arachnoid by a rapid accumulation of pus and bacteria. The center of such an abscess soon showed signs of necrosis and grew by addition of leukocytes to the periphery. The degree of resistance toward spread into the subarachnoid space was very high, and it was a common occurrence to find countless bacteria growing on the outer surface of the arachnoid membrane without being able to demonstrate a single organism in the subarachnoid space beneath. At such times the latter cavity was filled with leukocytes and the perivascular spaces emptying into this area were crowded with white blood cells.

When the subarachnoid space became involved it usually was filled with a coagulated exudate. It often reached a considerable distention as shown in Figure 2. Bacteria, leukocytes, and macrophages were distributed through the meshes of the pia-arachnoid. After the abscess had existed for several days, large cells with metachromatic granules, eosinophils, and plasma cells appeared on the scene. At this time the molecular zone was constantly (less often the deeper zones of the cortex) infiltrated with leukocytes, and the neuroglia cells gave evidence of proliferation. The bacteria, however, were sharply limited to the subarachnoid space, and only exceptionally began to break down the resistance of the pia mater and the molecular zone of the cortex, and to spread within the substance of the brain. It is interesting to note that only infrequently did the organisms grow into the perivascular spaces and invade the nervous tissue in this way. To repeat, the distribution of bacteria was confined by natural boundaries in the two limits of the subarachnoid space, that is, the pia mater and the arachnoid membrane. Infections spread through these thin connective tissue membranes only with great difficulty.

There was evident no natural barrier protecting the ventricles from invasion. As the growing abscess neared the ventricular wall, the ependymal lining of the latter was raised up by an exudate of serum and leukocytes. The character of the ventricular fluid was then so modified that it could be stained in section by eosin and toluidin blue. The fluid in the ventricle, which coagulated following fixation, showed no fibrin deposition. It contained a very few cells, mainly leukocytes of the mononuclear variety. The number of intraventricular cells increased with the steady progress of the bacteria toward the ventricle while the proportion of the polymorphonuclear leukocytes became augmented. The effort of the exudative cells to localize the process to the invaded portion of the ventricle was usually partly successful, and for a time only the ipsilateral ventricle contained a cellular exudate, but the rest of the ventricle was slightly dilated with a homogeneously stained fluid. As a rule, however, the infection spread throughout the ventricular system when once the bacteria gained access; the whole system became filled with organisms and pus cells. The spread through the foramina of Luschka and Magendie resulted in a basilar meningitis which extended rapidly down the cord and into the adjacent cisterns. During this invasion of the ventricle, the choroid plexus maintained a fairly normal appearance, although large areas of the parietal ependyma and subependymal tissue became excoriated. A few polymorphonuclear leukocytes infiltrated the connective tissue stroma of the choroid and the vascular plexus was slightly dilated; but in spite of the fact that the ependyma covering the choroid plexus was bathed in pus and bacteria, but little degeneration occurred. After a time the stroma became filled with a massive cellular exudate so that the plexus was greatly thickened. A few bacteria were found within the epithelial covering and the latter began to swell up and separate from the stroma. Shreds of detached epithelium could then be seen undergoing degeneration in the debris filling the ventricle. More often the death of the animal ensued before total destruction of the choroid plexus took place. Where the original wound communicated with the ventricle the entire ventricular system became quickly dilated with a compact cellular exudate and the sero-fibrinous character of the exudate was much less marked.

REPAIR

There were no experiments in this series which might be regarded as intermediate steps leading to the elimination of the process. Thirteen of the thirty-five animals died within forty-eight hours; sixteen died within a week but lived more than forty-eight hours, and three died nine days after the injury. There were only three that survived; these animals were killed at the end of two, three and four months, respectively. In the first instance, the cerebral lesion was irrigated with chloramin solution on several occasions, and the gross picture was that of a solid replacement of the destroyed nervous tissue by connective tissue without the usual formation of small cysts. In this specimen there were streaks of brilliant salmon pink radiating from the meninges down into the substance of the brain. The brains of the other two animals which survived showed cysts of various sizes on cross-section.

The original volume of the brain was much diminished where the wound occurred and the lateral ventricle showed a dilatation at this point (Fig. 4). In all three of these specimens the leukocytes had disappeared from the scene entirely. Strong bands of fibrous tissue arising from the fused dura and pia-arachnoid radiated into the area of destruction, carrying with them vessels from the meningeal system. Between this connective tissue replacement and the normal nervous tissue was a zone of gliosis. The phagocytic cells were still present in considerable numbers, being heavily laden with pigment. No glial cells could be found within the scar-tissue itself. The cysts were outlined by connective tissue and were often filled with macrophages. Often these cavities were in direct communication with the perivascular space. In one of the animals, the scar tissue replacement showed that the lateral ventricle had been penetrated, but the break in continuity of the ventricular boundary had been subsequently sealed over completely. None of the cystic dilatations around the perivascular spaces communicated with the ventricles. The ependymal lining at the end of four months had not yet begun to cover up the defect caused at the time of injury. The pattern of the subarachnoid tissue spaces was carried into the defect from the outside (Fig. 4), and resulted in a considerable widening out of the subarachnoid space at this point. None of these cystic enlargements seemed to communicate with the subarachnoid space. Every one of the animals which survived the infection showed a healed process in every way comparable to the healing of a sterile ablation of a similar amount of brain tissue. In none of them was found a walled-off process similar to the chronic abscesses encountered in extensions from the middle-ear or the solitary encapsulated abscesses in human beings.

DISCUSSION

The problems confronting us in acute traumatic abscesses of the brain are primarily two: (1) the factors influencing the development of a destructive bacterial invasion of the brain, and (2) a repair of the lesion. The first comes under the head of inflammation, while the latter has to do with the re-establishment of a viable organism. Concerning the repair of brain lesions, considerable experimental work has been carried on, and the histology of the events leading to the establishment of a physiologic equilibrium is fairly well understood. A complete restoration of destroyed nervous tissue is never attained. and even in new-born animals the nervous system is too completely differentiated to reproduce any new elements. Function can be partially taken over by other cells, and when confined to certain areas of the cerebral cortex a normal individual, to all intents and purposes, may be preserved. The final repair is almost exclusively a partial replacement by connective tissue accompanied by a new ingrowth of vessels and to a very slight extent by the neuroglia which interposes a zone of sclerosis between the fibrous scar and the normal nervous tissue. An understanding of the factors involved in the destruction of the nervous elements, along with the efforts to halt its spread and the removal of the debris, namely, inflammation, will give us a clue to a rational therapy.

Experimentation which would show only the processes concerned in inflammation to the exclusion of those concerned in repair is manifestly impossible. Every experiment in inflammation must, of necessity, include a varying mixture of both these phenomena in the same specimen. On the one hand must be considered the bacterial agent elaborating toxins which diffuse into the tissues; the effect is not limited to the area directly reached by the poison but extends for a great distance by secondary degeneration of the affected neurons. On the other hand, there are the countless defensive cells poured out from the vessels in an effort to halt the spread of the destructive agents; the removal of dead material by the cells of the macrophage class; and finally, the reparative efforts of the young fibroblasts. All of these processes are intermingled and exist in varying proportions in different localities of the wound. In addition to these generalizations, there must be taken into account the factors peculiar to the central nervous system — absence of fascial planes, the effect of the chemical constituents of the degenerating tissue, the ease with which the brain can distend, and the effect of the rigid envelop which permits of little expansion — in a word, the anatomico-physical characteristics of the affected organ.

The division of the pathologic process into three zones serves a useful purpose in presenting the microscopic description in a more or less orderly way. As an active process, another kind of division would perhaps furnish us with a more logical conception of a traumatic brain abscess. This would consider but two zones: (1) a central necrotic foreign body, the source of soluble toxins, and (2) a peripheral zone in which the struggle between two opposing forces takes place. In this latter zone, which is a combination of the zone of cellular exudate and necrobiotic zone, the course of the abscess is determined: the termination may be either (1) a losing fight in which the animal as an organism succumbs, or (2) a retardation of the spread until a connective tissue capsule may be formed, or (3) an actual neutralization and elimination of the bacterial agent. In these infections where the streptococcus was present, the central core became in every sense a foreign body. Encircling this the organisms grew luxuriantly and formed the reserve depot from which a spread forward could be made in case the tissues were sufficiently weakened. The outer zone represents the vascular changes and associated exudation met with in inflammation. The diffusion extends from the central mass into the periphery, with a progressively weaker effect as it diffuses from the point of elaboration. The structural tissue is killed or damaged and the blood vessels become unable to hold within their walls the fluid and nonameboid elements. This zone of exudate and hemorrhage becomes the arena in which the fate of the animal is determined. If the virulence of the organism is lower than the combined resistance of cellular exudation and development of antitoxic bodies, then the so-called zone of "red softening" turns progressively to one of a salmon yellow, and finally, to one of brown color. If the relative strengths of the infection and resistance are reversed, the bacteria grow forward into the outer zone which is progressively incorporated into the necrotic center. In some types of infection the tendency of the red cells to spill out into the tissues is not marked. Just how this factor modifies the spread of the infection will be discussed later. The ecchymosis of red corpuscles is in all probability a weak chemical protection and ought not to be considered as a part of a preparation for the formation of a purulent inflammation. The notion that an abscess is always preceded by "red softening" gives a false impression in that it makes the effect appear to be the cause. In no wise does it help our conception of the processes going on in the development of a purulent focus. The evidence points away from the idea that red softening is in any way a "preparation" of the nervous tissue for the development of an abcess.

The kind of infection used in these experiments may be considered under two heads: (1) pure cultures, and (2) pus. The former always proved to be the weaker in virulence, while the latter probably owed its destructiveness to the associated agressins. By passing the pus from the cortex of one animal to another, a rapidly fatal lesion could be produced, with death within twenty-four hours. In these instances the effectiveness of the toxin was shown in the widespread "burnt-out" appearance of the tissue as well as the uninterrupted advance of the organisms. Their distribution was more or less uniform throughout the abscess and extended for a short distance beyond the cellular exudate into the zone of necrobiosis. When the virulence was not so great, the bacterial invasion was sharply confined to the central zone of necrosis. The failure to spread invariably into a purulent meningitis from the point of injury is interesting. Rarely does the subarachnoid space contain organisms at any considerable distance beyond the lesion. On the other hand, the subarachnoid space or brain tissue may not be involved even when the subdural accumulation of pus reaches enormous proportions. The occurrence of a leptomeningitis follows much more often a spread from the ventricles through the foramina in the hind-brain. This spread into, or direct inoculation of, the ventricle is one of the most serious complications of a brain abscess.

The natural resistance to the spread of infection is very inadequate. The only barriers at all comparable to the fascial planes elsewhere, are the meninges. The essential elements taking part in this protection are the cells making up the pia-arachnoid. Their behavior toward debris introduced into the subarachnoid space has demonstrated the active rôle played by these mesothelial cells. Under the stimulus of products of tissue destruction, they proliferate and give rise to ameboid mononuclear cells with marked phagocytic powers (Essick[14]). Figure 17 shows them massed at the glued edges of the meninges bordering a brain abscess. By removing the destroyed tissues they help to keep the meningeal spaces open so that a circulation of cerebro-spinal fluid is possible. The abscesses following extension from the air sinuses (middle ear, frontal, etc.), meet with a definite obstruction in the dura, but the more cellular leptomeninges are extremely resistant to a spread at right angles to their plane. The delicate arrangement of the closely interweaving fibrils in the pia mater and the arachnoid membranes keeps the process on either side of them very sharply localized. Thus an encephalitis is halted at the pia and prevented from becoming an uninterrupted meningitis; a subdural abscess is similarly checked by the arachnoid membrane. The massive growth of bacteria beneath the dura may not only cover a large part of one hemisphere, but also extend beyond the mid-line beneath the falx-cerebri, and yet if one searches carefully it may be impossible to find a single organism within the cellular exudate in the subarachnoid space, whereas the outer surface of the arachnoid membrane is literally covered with them. To be sure, this resistance may be broken down, but only after the tissues have been grossly insulted. The normal amount of connective tissue within the substance of the brain is almost negligible, being confined to the thin sheaths of the vessels.

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[14] Essick, C. R.: Formation of Macrophages by the Cells Lining the Subarachnoid Cavity in Response to the Stimulation of Particulate Matter, Carnegie Institution of Washington, Publication 272, 1919. Contributions to Embryology, **9.**

The rich, close-meshed capillary plexus within the gray matter may be one factor in determining the relatively greater resistance of the gray matter to infection as compared with the white matter. The latter is provided with a system of elongated capillary loops so that the blood supply is very much poorer than in the cellular layers. This disparity in resistance of gray and white matter is further heightened by the fact that the central end of an injured neuron may live, but the peripheral end always dies. The nuclei of the cells making up the fiber tracts are situated largely in the cortical gray and the secondary degeneration in the peripheral end of the nerve fiber furnishes a good culture medium for the bacteria.

The most efficient protection for the substance of the brain is that supplied by the leukocytes which pour out into the perivascular spaces around the injury and quickly form a cellular barrier against the spread of the infection. Probably the injury to the tissues is the primary stimulus in the case of the ordinary infection, but shortly after an absorption of the toxic substances makes increased demands on the white blood elements. Long before any antibodies may be formed, the bacteria have created quite an area of necrosis at the point of injury. The blood vessels become dilated and enormous numbers of leukocytes crowd the perivascular spaces. White blood cells emigrate from all the small vessels in the neighborhood and crawl toward the lesion, preferably along the perivascular spaces. If the infection be entirely meningeal, the perivasculars are transformed into veritable crowded highways by the white cells hurrying toward the subarachnoid space. Such "perivascular exudate" should not be viewed as an invariable sign of encephalitis, but rather as the natural pathway for inwandering cells. These perivascular spaces would make excellent natural channels for the spread of organisms through the nervous tissues were it not for the fact that the advance of the bacteria is very early blocked by the cells coming into these perivascular channels from the blood-stream. Occasionally one comes on a vessel that has become thrombosed, and then it furnishes an excellent pathway for the spread of the bacteria. Inasmuch as the leukocytes in such a case do not continue to come out of the vessels into the perivascular spaces, the latter become literally filled with colonies of bacteria (Fig. 9). The leukocytes, then, both of the polymorphonuclear and the small mononuclear variety, are the best protection that the brain may acquire quickly. The predominating type of cell cannot be predicted, and the variety of the cell seems to be entirely independent of factors under control.

There is unquestionably some development of antibodies in the blood stream, but in this type of abscess, protection from such a source must be a small factor in overcoming the process. A far better chemical protection is to be found in the escaping whole blood which occurs in the necrobiotic zone in considerable quantities. The efficacy of this mechanism has been demonstrated in several ways in this series of experiments. In one animal in which a button of bone was pushed into the wound it was seen at necropsy that a very large hemorrhage had developed (Fig. 16). Microscopically, this portion of the injury proved to be absolutely unaffected by the infectious process, although this had involved a considerable amount of the cerebral hemisphere Not only does such an area of hemorrhage remain uninvaded by the organisms in the midst of so much infection, but also the extravasated corpuscles are actually being removed by the phagocytes while young fibroblasts and blood vessels sprouts are beginning to repair the defect. Another remarkable instance of the protective powers of blood is shown in Experiment 66. Owing to the scarcity of animals when experimental abscesses were made, a good many of the cats had to be used for more than one observation. After each experimental procedure they were allowed to live for several weeks and to regain their "normal" appearance. After serving as the subject of three experiments on the central nervous system and recovering, this cat, while under ether, was struck on the head with a sharpened nail and the wound infected. Gross necropsy showed that the puncture had been made so close to the mid-line that a large meningeal vessel had been opened up and a hemorrhage had covered the left cerebral cortex for at least 2 cm. from the brain wound. There was no evidence anywhere of a meningitis macroscopically. The animal had lived for three days, and when studied microscopically showed an extensive destruction of brain tissue. The bacteria were growing in enormous numbers along the natural pathways in the nervous tissue. There was no cellular zone visible under low magnification, and with higher powers, a few inwandering polymorphonuclear leukocytes were observed as single cells, scattered around the edges of the abscess. Apparently, the previous experimentation had in some way broken down the responsive cellular exudate and the bacteria proliferated within the brain much as if they had been planted on cultural media. In this instance the lesion was absolutely localized to the substance of the brain, and not a single organism could be found growing within the subarachnoid space. The whole blood formed a perfect barrier against a spread of organisms in the meningeal spaces and constituted the sole protection against a meningitis.

Most of the experimental abscesses were marked by a varying tendency to ecchymosis. The actual number of red blood corpuscles was usually not great. Such small accumulations of erythrocytes offer a momentary obstruction to an uninterrupted advance of the infection. The more susceptible areas allow the infection to work around the sides of the blood extravasation. Thus in Figure 7 the perivascular hemorrhage stands out as a salient, retarding the line of advancing bacteria. Finally, such accumulations of red corpuscles are completely surrounded and gradually are included in the necrotic core. This may help us to understand the value of the treatment of penetrating wounds of the brain at the battle front. The best results have followed extensive lavage of the tract and tight closure of the wound. The chemical value of hemorrhage seems to lie in the red blood corpuscle rather than in the serous or the fibrinous exudate.

Of certain value is the relief of pressure developing in a confined space. Increase of brain bulk is unquestionably the beginning of a vicious circle and is the worst complication which follows a traumatic infection. The method of combating the rising pressure within the brain by opening the skull and dura has been employed by surgeons for a long time. Certainly, it prevents the dislocations if enough outlet is given to the expanding brain, as is seen in Figure 19. The most distressing feature follows the trephining of the skull and the formation of a sloughing and infected fungus. It is to be hoped that the reduction of brain-bulk following the alteration of the tonicity of the blood will give a practical method of removing the cause, instead of trying to combat the effect. A very suggestive method of modifying the development of edema and its correlated increase in intracranial pressure may be found in the work of Weed and McKibben.[15] It may be that the effects of trauma can be overcome by suitable intravenous injections of hypertonic solutions of salt or dextrose, and the phenomena of swelling be temporarily, at least, if not permanently obviated.

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[15] Weed and McKibben: Experimental Alteration of Brain Bulk, Am. J. Physiol. **48**:531 (May) 1919.

The factor of injury in traumatic abscess of the brain is most important from two standpoints. The most obvious is the destruction of brain-continuity and its associated secondary degeneration. Less obvious, but more important, is the swelling of the injured portion of the brain following such injuries. The most careful manipulation of the normal brain is sufficient to set in motion the factors increasing the size of the organ. These causes are little understood, except for the general concept of disturbance of balance of the tissue fluids, the intercellular, cerebrospinal and intracellular fluid. Edema of the brain, when the skull and dura are unopened, causes a rise in pressure of the contents of the cranium and must facilitate the thrombosis of vessels in the injured area. The actual blood supply is seriously interfered with at a time when there should be a protective hyperemia. The resultant dislocation of so delicate a mechanism caused by the swelling of one region and a compression of the rest is a most serious complication. Added to this phenomenon is a ventricular dilatation which further reduces the available space for normal tissue. Such a complex results in an increased susceptibility to destruction where a bacterial agent is present, and serves to prolong the edematous condition initiated with the original wound. The relief of such a condition by trephine merely transforms one complication into another which is little less of an evil. The infected hernia seems to have no end to the possibility of expansion. It cannot be too strongly emphasized that this phenomenon of injury, and its associated swelling, is the essential difference between traumatic brain abscesses which run such an acutely destructive course and the slow-growing abscesses which extend from the air passages. Operative procedures aimed at the cure of the slowly growing abscesses must scrupulously avoid all unnecessary disturbance of the healthy brain tissue, lest they excite the phenomena of brain swelling and transform the chronic abscess into an acute traumatic one.

The products of secondary degeneration of the fiber tracts offer an excellent medium for the culture of bacteria. The presence of the fatty derivatives of myelin must have a decided influence on the growth of the organisms as well as retard the interchange of fluids between the necrotic center and the surrounding tissues. These experiments with foreign bodies were too few to draw any conclusions as to their effect on the progress of an abscess. Infection of the ventricle seems to bear no relation to the general reaction of the animal, whether inoculated directly or becoming involved by a secondary spread. In the thirty-five experiments recorded here, the length of life seemed to be governed by the virulence of the infection. One of the cats surviving the infection showed that the original wound had penetrated the ventricles and reached the surface of the cortex on the side of the brain farthest away from the entrance of the perforator.

As far as can be determined the nervous tissue has practically no natural planes in which infection may spread with greater difficulty. The neuroglia forms a feltwork which makes the gray and white matter practically homogeneous. Secondary degenerations furnish a decrease in resistance, but this cannot be looked on as preformed. The perivascular spaces are natural channels which can be invaded by bacteria. Unless the normal protective mechanism is disturbed, either by interfering with the response of the white blood cells, or by thrombosis, such channels cannot be entered by the bacteria. The spread of an infection occurs by direct destruction of the tissue assisted by the secondary degenerative processes formed by nerve fibers separated from their cells of origin.

Mingled with the processes of destruction and protection are cells whose main function is to remove the debris. The large phagocytic cells appearing in such enormous numbers in the central nervous system were regarded by the early writers as pathognomonic of inflammation. In no inflammatory process elsewhere in the body do they appear in like numbers. The formation of such large phagocytic elements from the cells of the arachnoid, from those of the vascular adventitia and from neuroglia cells has been demonstrated to occur under the influence of altered environment. These transformed cells gather in the region just beyond the zone of leukocytes as long as the infection is active, greedily ingesting the free red cells, dead leukocytes, and products of destruction of the nervous tissue. If the organisms are killed and their toxins neutralized, these macrophages invade the necrotic core and remove it. Long after the last leukocyte has left the scene these large cells are found in great numbers, with their bodies distended with ingested material. The removal of the debris is exceedingly slow in the brain, since it depends entirely on the ameboid activity of these large mononuclears. The lack of a lymphatic system, which, in the infections of the tissues of the body generally, plays an important rôle in the removal of waste products of inflammation, may easily account for the increased demand for these cells in processes involving destruction of the nervous system. Where the abscess spreads rapidly, these phagocytes appearing beyond the leukocytic wall are destroyed, and as a result, few are demonstrable in this type of lesion. Where the extension is slow, or where the rate varies considerably in different localities of the same abscess, these cells are often found in such numbers that they almost replace the normal structures.

The attempt to repair the lesion is instituted within the first few days. Such repair is entirely brought about by the fibroblasts and new vascular sprouts. They are the derivatives of the meningeal mesothelium and of the adventitial cells of the blood vessels. In the slowly growing abscess these efforts are partially successful and a capsule is formed and serves to retard the spread of the process to a marked degree. This mechanism is too slow to be of any assistance in stopping a traumatic abscess. These fibrous elements form, however, the tissue which replaces the lost structures, if the infection is overcome. This fibrosis of the defect is, however, frequently complicated by the formation of cysts in the scar. These develop as dilatations of the perivascular spaces and are to be explained as accumulations of intramedullary cerebrospinal fluid, the free drainage of which has been interfered with (Pick[16]). The superficial defect of the brain is partially filled by an increased development of the subarachnoid tissue, the meshes of which are in free communication with the rest of the cerebrospinal fluid spaces.

SUMMARY

Experimental abscesses produced in the cortex of thirty-five cats by injury and infection of the brain, resulted in a rapidly fatal process which simulated the traumatic injuries of the central nervous system in man. The affected part enlarged and brought about a marked dislocation and compression of the rest of the nervous tissues. In 50 per cent. of the cases the infection reached the ventricular system within a few days, and from there usually spread into a basilar meningitis through the metapores of the fourth ventricle. The tendency of the infective process to invade the subarachnoid space from the point of injury was not marked, but in a third of the animals the infection entered the subdural space, forming there a subdural abscess.

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[16] Pick, A.: Ueber cystöse Degeneration des Gehirns, Arch. f. Psychiat. u. Nervenh. **21**:910, 1890.

These lesions were very different from the more slowly growing abscesses extending from the air sinuses. The latter, occurring frequently in man, may be differentiated by the relatively slight swelling and dislocation, and by the development of a definite connective tissue capsule between the lesion and the sound parenchyma. The traumatic abscess in the experimental animal extended rapidly along the fiber-tracts. No encapsulation could be demonstrated in any of these observations. Healing took place by the ingrowth of connective tissue.

Plate 1—Explanation of Figures.

Fig. 1.—Photomicrograph. Abscess of three days' duration, confined almost exclusively to the fiber tracts. The center was occupied by a large bubble of gas. An extensive subdural abscess is complicating the brain lesion. (Hem.-eosin, × 3.7.)

Fig. 2.—Photomicrograph through the leptomeninges immediately adjacent to the abscess. An early stage of meningitis accompanied by an extensive serofibrinous exudate. The perivascular spaces of vessels penetrating the cortex are crowded with leukocytes. (Hem.-eosin, × 72.)

Fig. 3.—Photomicrograph of the brain tissue just beyond the leukocytic zone (top of figure). The perivascular spaces are engorged with leukocytes, practically obliterating the lumen of the vessels. (Hem.-eosin, × 77.)

Fig. 4.—Photomicrograph—healed abscess. Dura adherent to defect in cortex. Small cysts are located in the connective-tissue replacement. Lateral ventricle dilated under the injury. (Hem.-eosin, × 3.)

Fig. 5.—Retouched photograph of head of cat in which cerebral hemispheres are partially exposed; the dura is intact. The injury appears in the dark area of the left hemisphere. The brain markings are obliterated on the affected side by a thick purulent subdural exudate. This is sharply limited, medially, by the falx cerebri. The right hemisphere shows engorgement of blood vessels with a very slight loss of distinctness of brain markings. (× 1.)

Fig. 6.—Photomicrograph. Left side of picture—zone of leukocytes. Middle shows a layer of extravasated erythrocytes interposed between the lesion and the normal tissue (on the right). (Hem.-eosin, × 60.)

PLATE 1

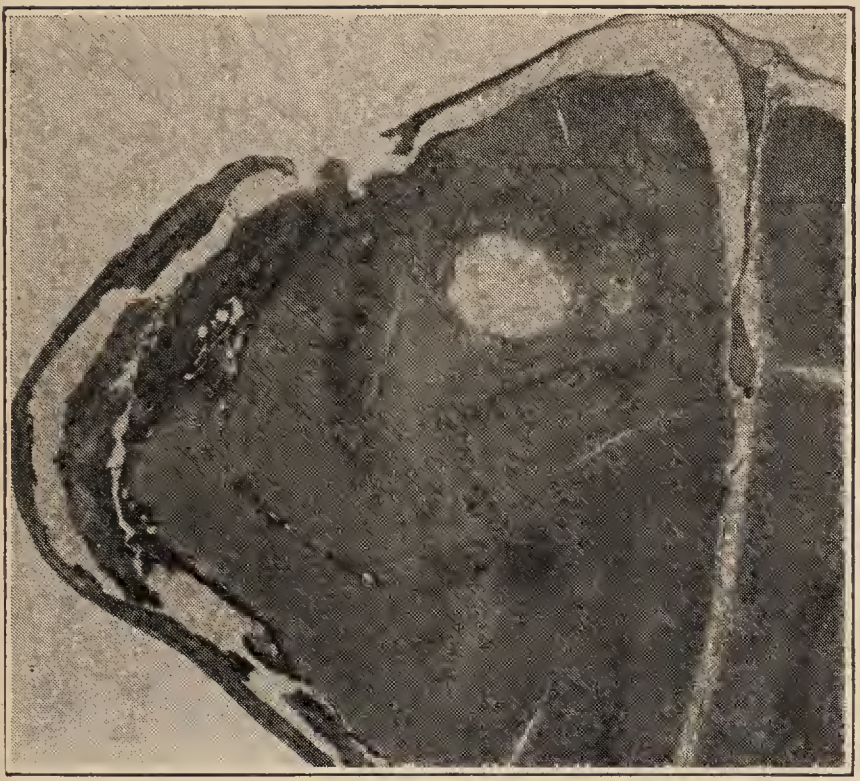
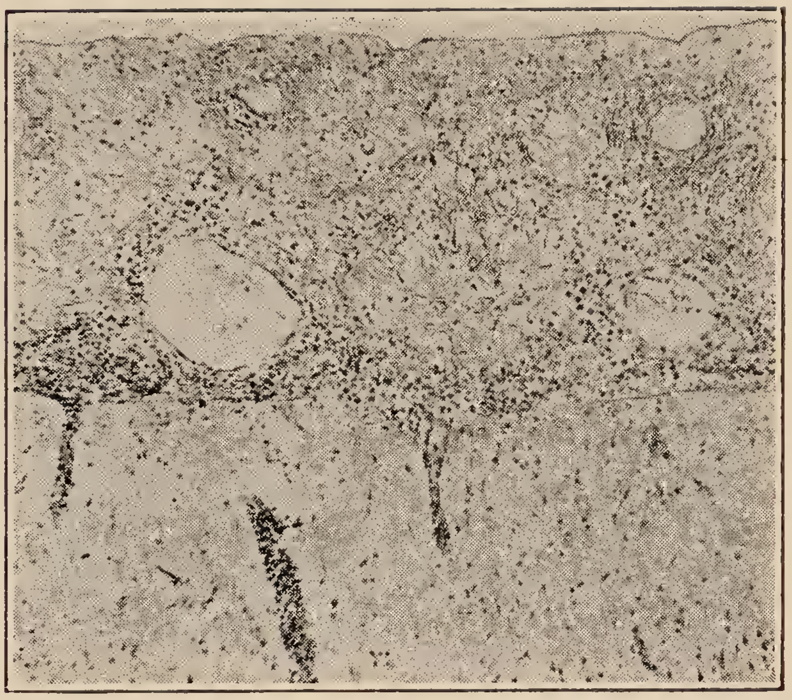


Fig. 1.



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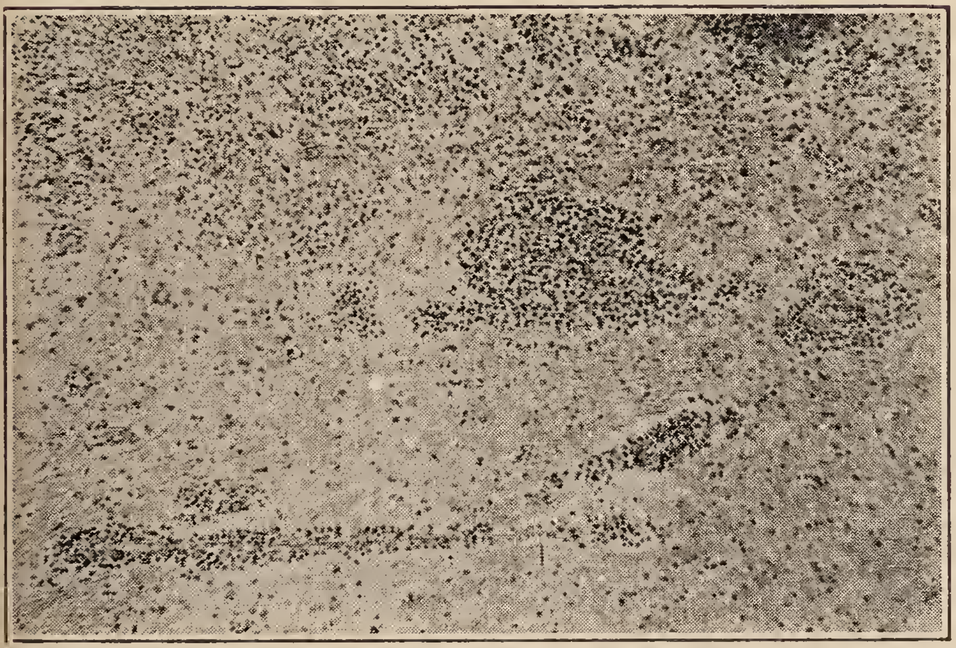

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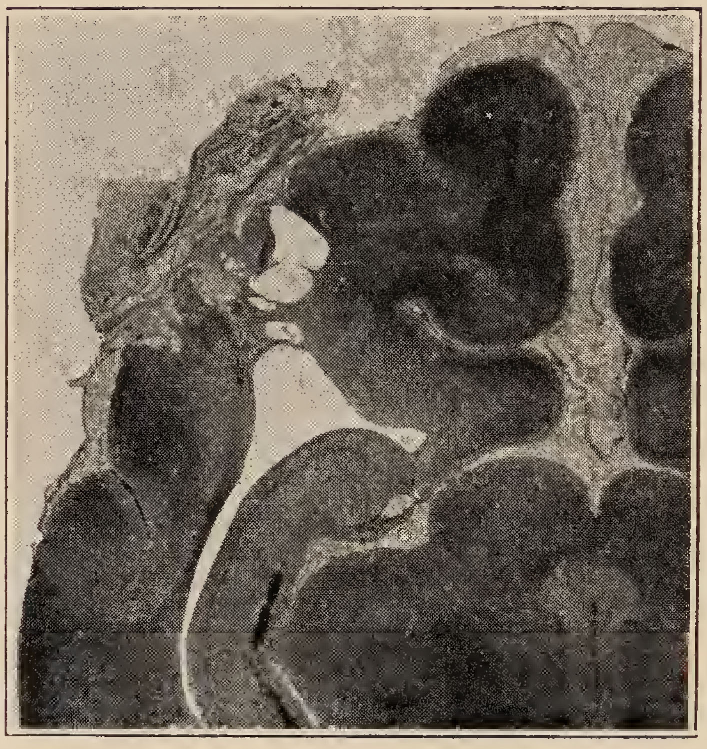

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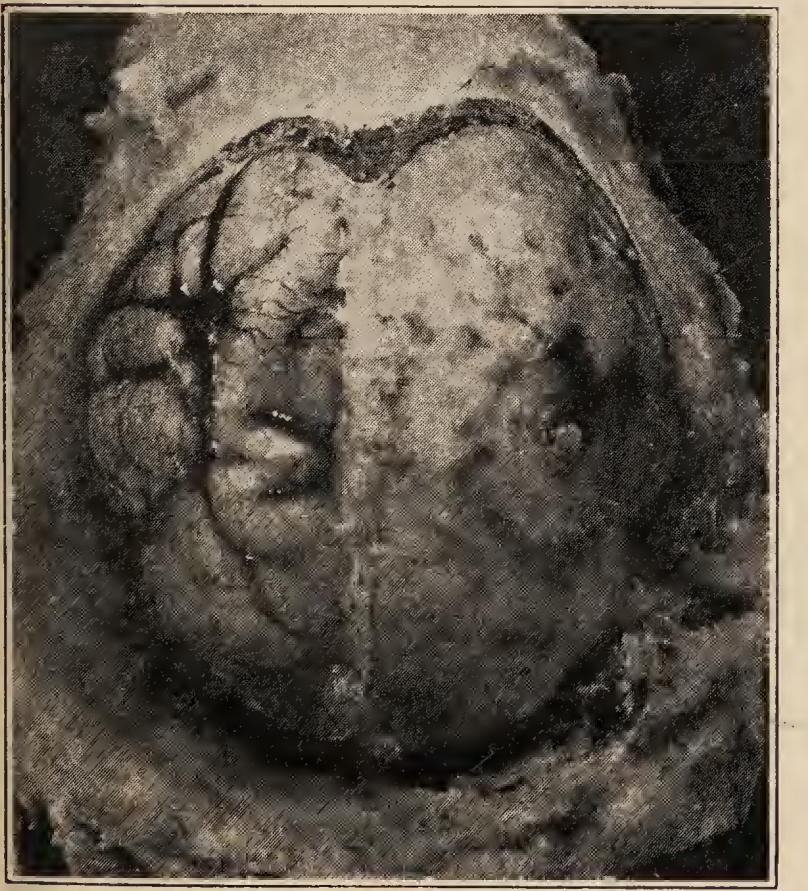

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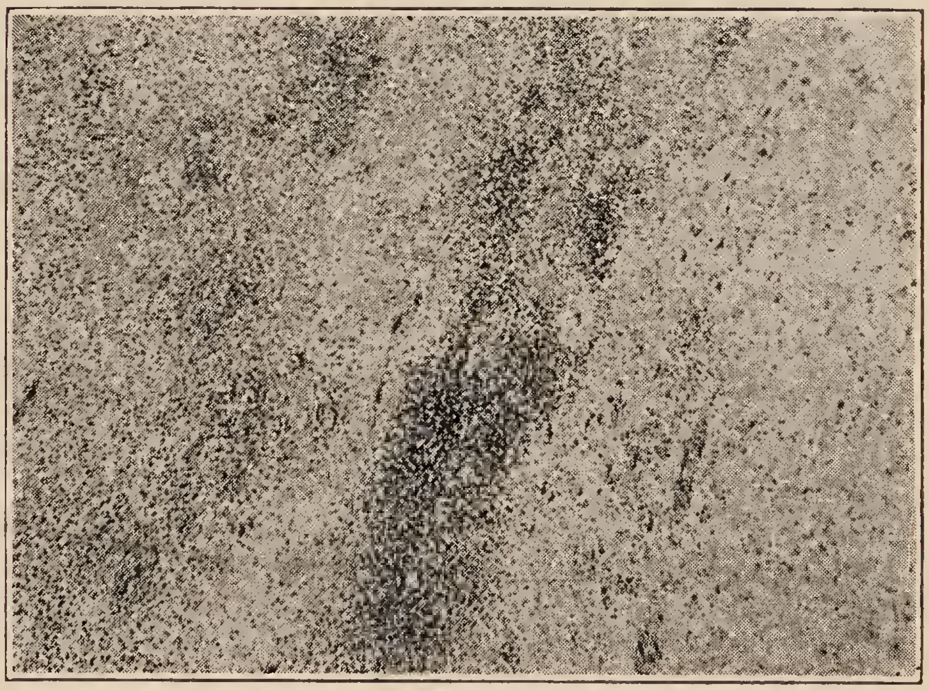

Fig. 6.

Plate 2—Explanation of Figures

Fig. 7.—Photomicrograph. The center of the figure shows two vessels, the perivascular spaces of which are filled with red blood corpuscles. The infection is momentarily halted at this point but the organisms are out-flanking them on both sides; separated from the normal tissue (right side of figure), however, by a wall of leukocytes. (Hem.-eosin, × 60.)

Fig. 8.—Compression and dislocation of brain by a large subdural abscess. The left lateral ventricle is slightly compressed and the right correspondingly enlarged. The white fiber tracts on the left side show the early development of a translucent gray core. (Drawing × 1.4.)

Fig. 9.—Photomicrograph of abscess showing the rapid extension of the bacteria when unimpeded. All the darker masses represent conglomerate colonies of organisms — completely filling the perivascular spaces. (Hem.-eosin, × 60.)

Fig. 10. — Photograph of sections through a brain in which a rapidly developing abscess of two days' duration has spread into the ventricle. The left lateral ventricle is distended with inspissated pus while the right is dilated with a clear coagulum. This shows a remarkable dislocation of the left hemisphere and a compression of the right. (× 1.2.)

PLATE 2

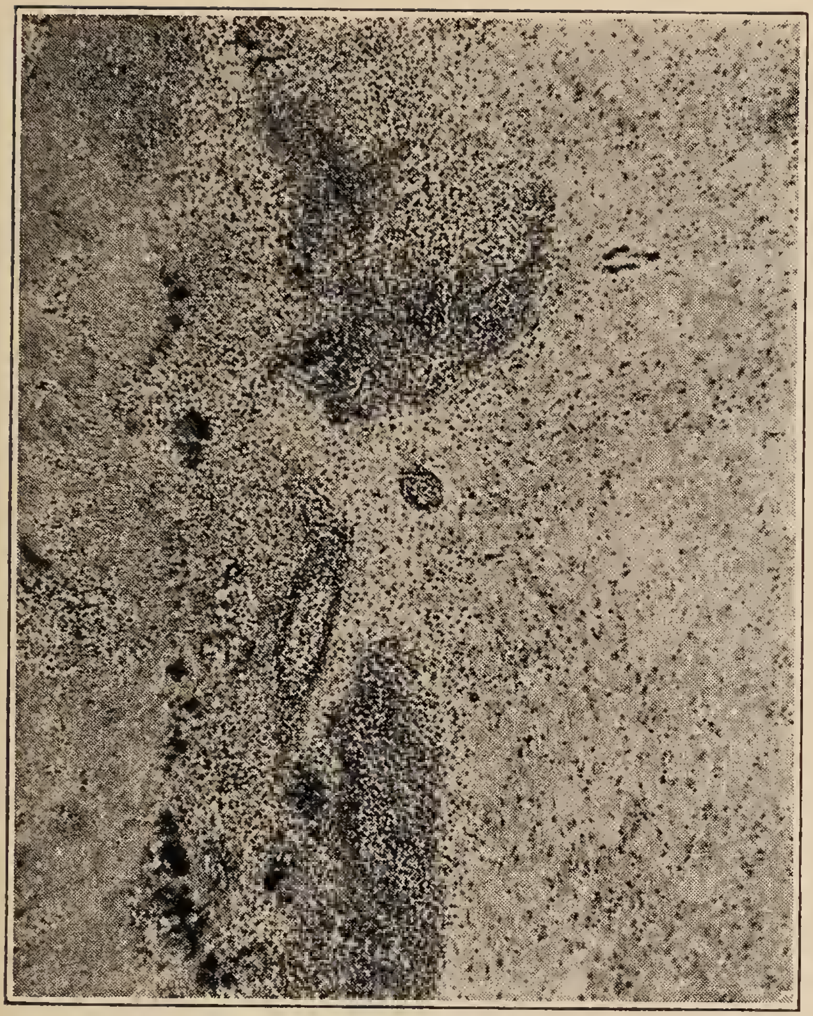

Fig. 7.

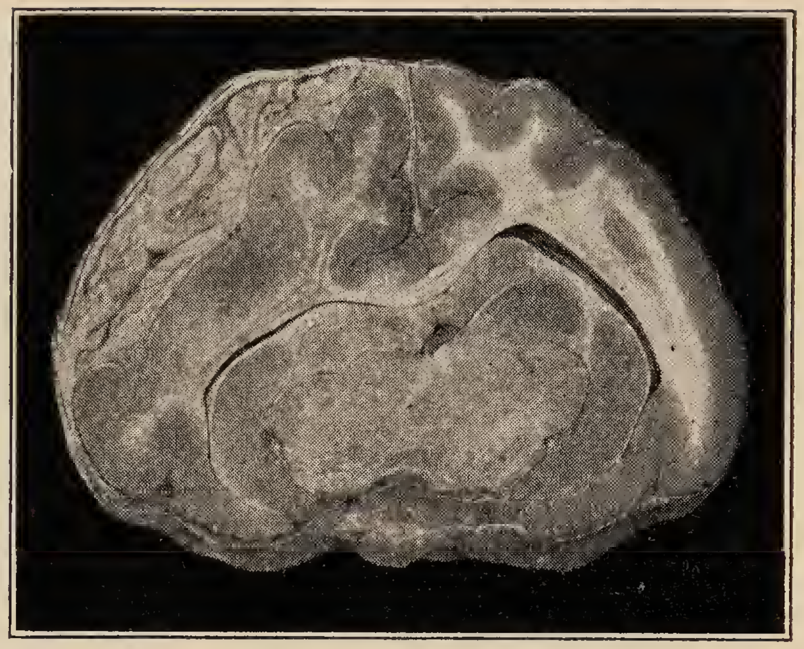

Fig. 8.

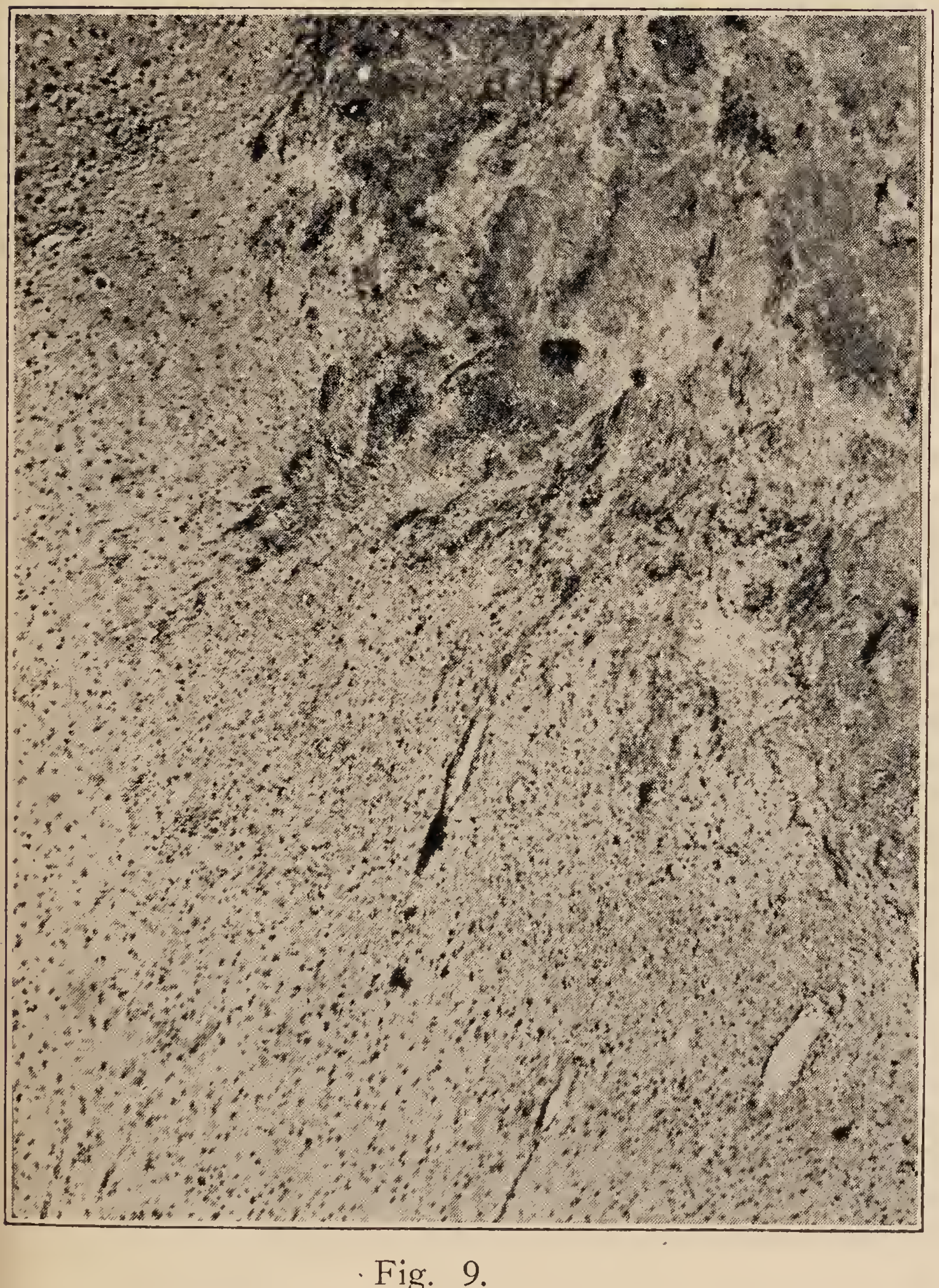

Fig. 9.

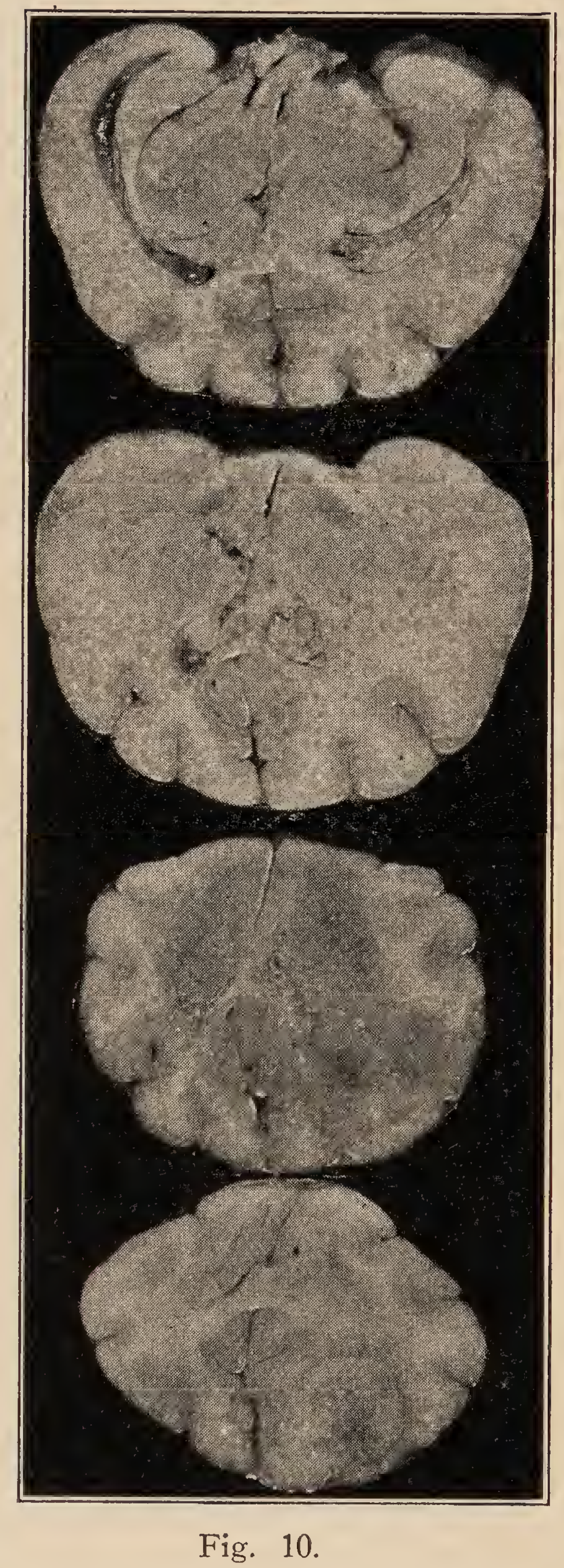

Fig. 10.

Plate 3—Explanation of Figures

Fig. 11.—Photograph. Sections through cat's brain showing the invasion of the fiber tracts by an abscess. This lesion is accompanied by a blood-tinged exudate and photographs black. (× 1.2.)

Fig. 12.—Cyst forming within an abscess. The entire white matter is translucent on the affected side so that the distinction between cortex and fibers is almost obliterated. (Drawing ×1.2.)

Fig. 13.—Photomicrograph. The spread in extremely rapid as shown by the thickness of the zone of leukocytes. In this specimen bacteria actually are found beyond the sharply delimited wall of leukocytes. Death of animal occurred in three days. (Hem.-eosin, × 60.)

Fig. 14.—Photomicrograph showing the lamination of a slowly developing abscess and the predilection for the white fiber tracts. The three indentations in the periphery of this process are the seat of perivascular hemorrhages. The large subdural abscess has separated from the leptomeninges. (× 3.9.)

Fig. 15.—Photomicrograph showing the grouping area of organisms and their mode of breaking through the leukocytic defense. The upper part of figure is the necrotic core. Extending in two broad columns are the two waves of bacteria; the one on the left is separated from the necrobiotic zone (bottom of figure) by a very few leukocytes. (Hem.-eosin, × 60.)

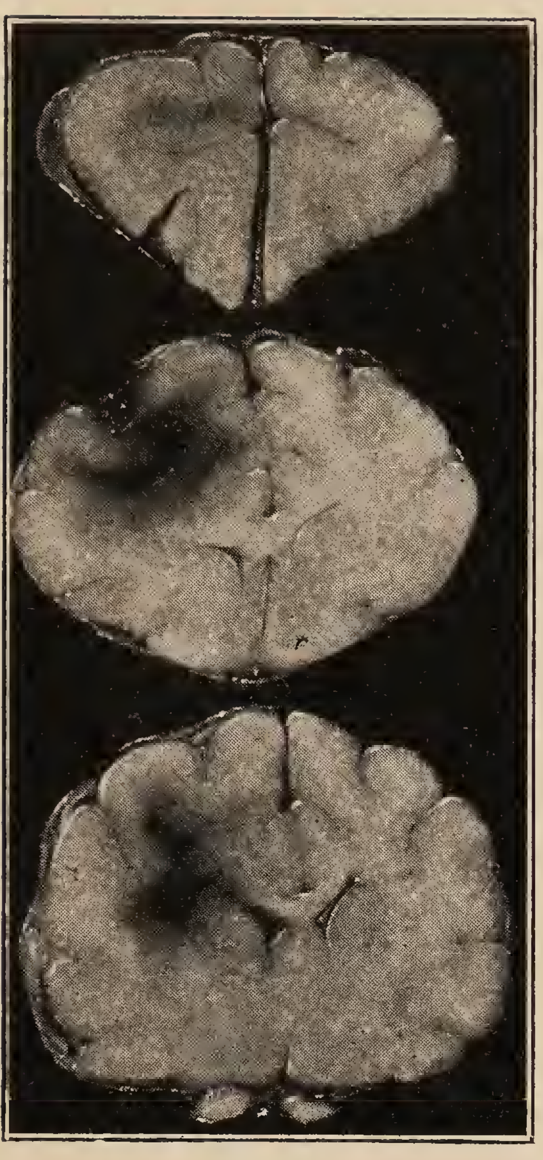

Fig. 11.

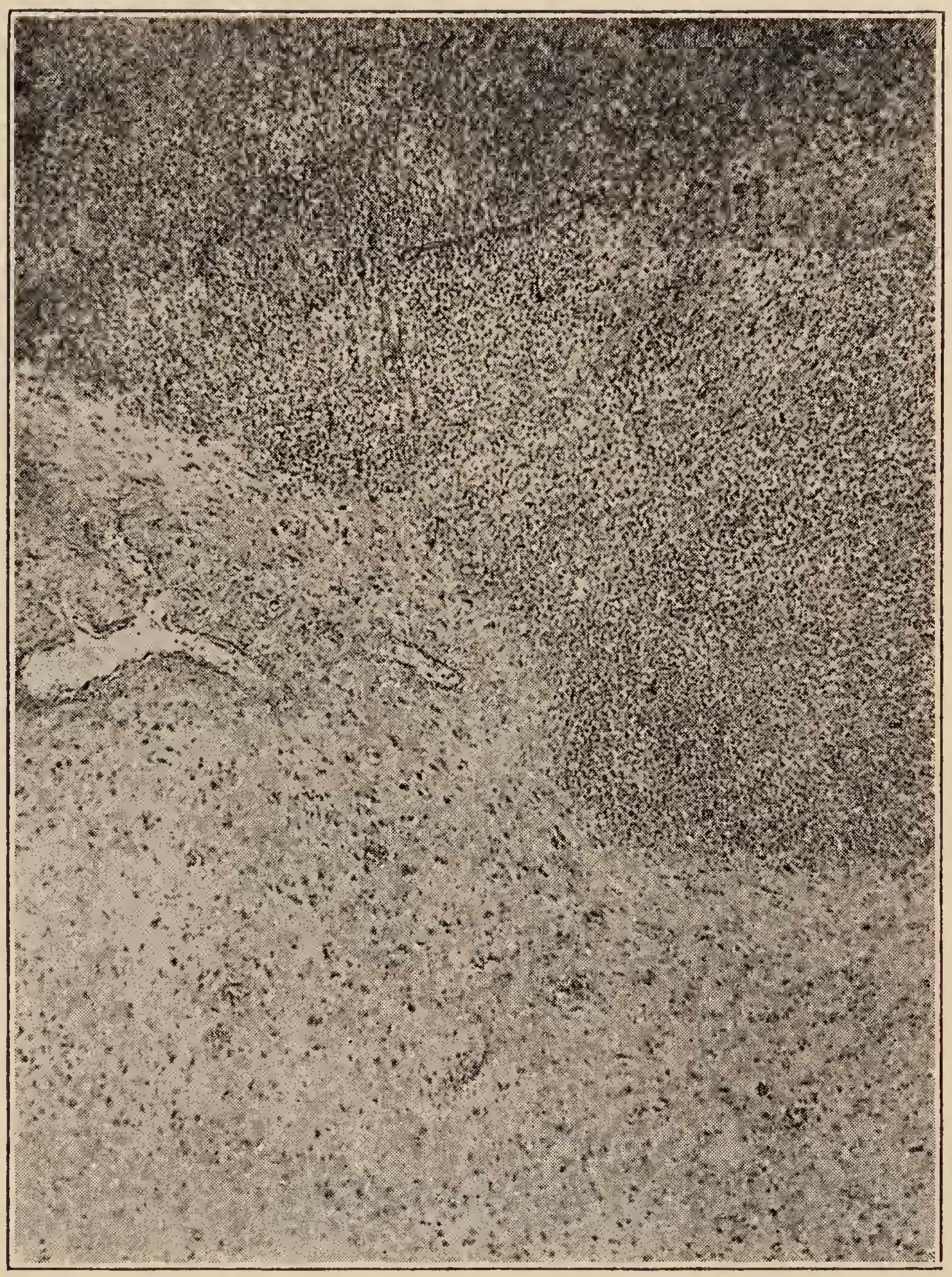

Fig. 13.

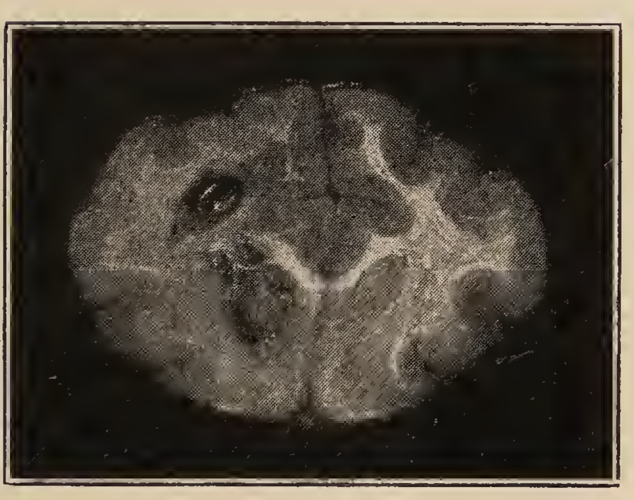

Fig. 12.

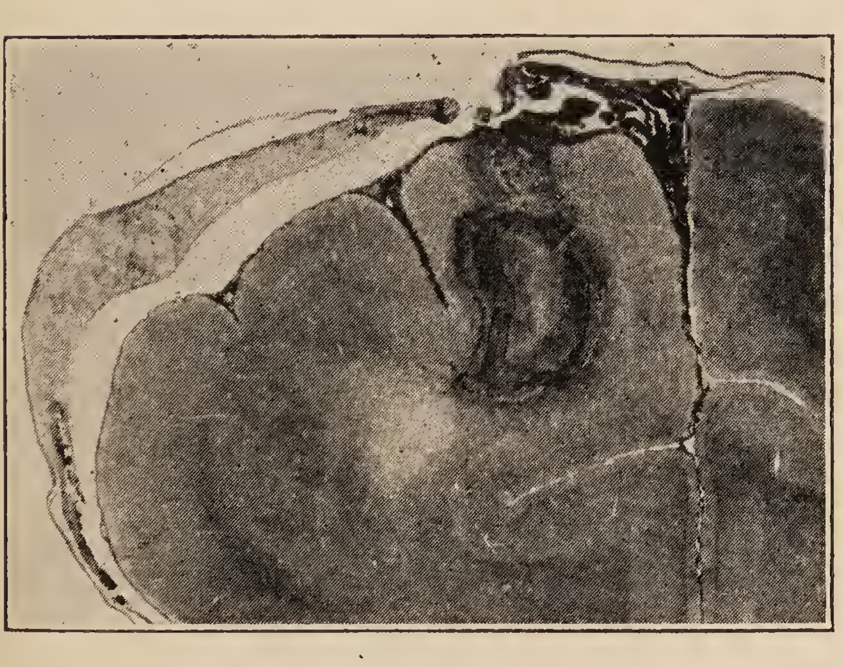

Fig. 14.

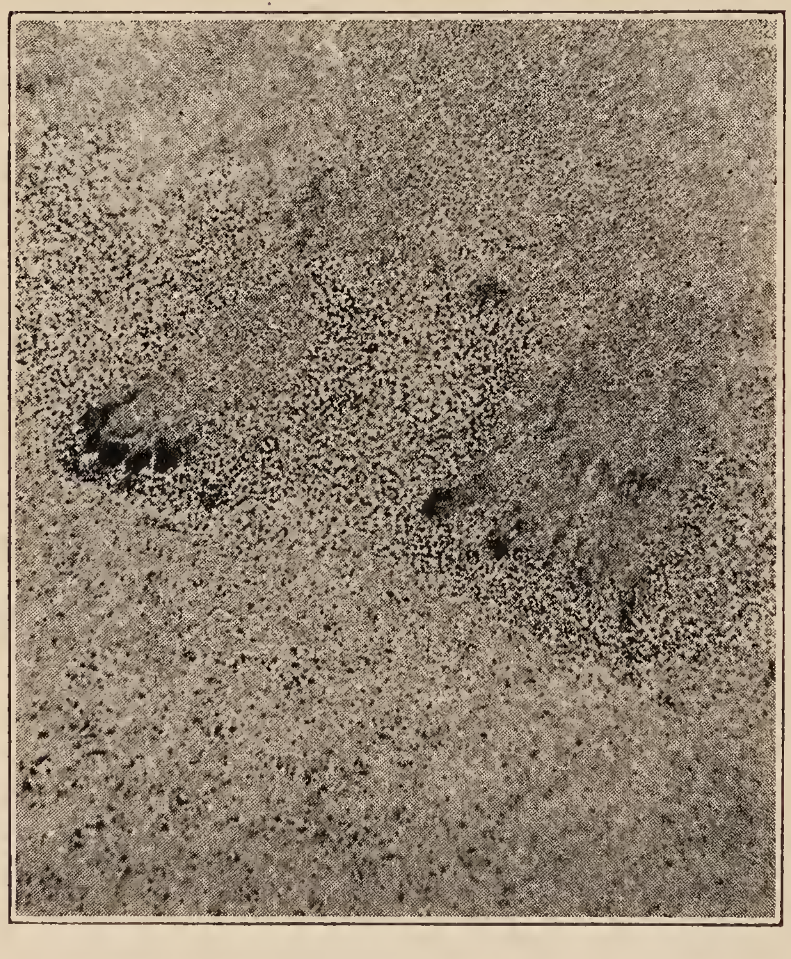

Fig. 15.

Plate 4—Explanation of Figures

Fig. 16.—Photomicrograph of a transverse section through entire cortex of cat. The abscess has developed within the white fiber tracts and into the thalamus. An extensive hemorrhage at the base made an efficient barrier to the spread in this direction. A large part of the blood has already been removed. This process lasted nine days. (× 3.3.)

Fig. 17.—Photomicrograph of a wall of macrophages derived from the pia-arachnoid which is shown blocking the subarachnoid space and preventing the destructive infection (upper part of figure) from spreading into a meningitis. (Hem.-eosin, × 60.)

Fig. 18. — Photograph of section of cat's brain in which the original wound communicated with the ventricular system. The lateral ventricles are dilated with pus. (× 1.4.)

Fig. 19.—Section through abscess developing under a trephine hole made in the skull. Remarkable hernia of left side of brain. The displacement is very great on account of a rapidly developing subdural abscess. Right hemisphere not compressed, as shown by midline. Six days' duration. (× 1.3.)

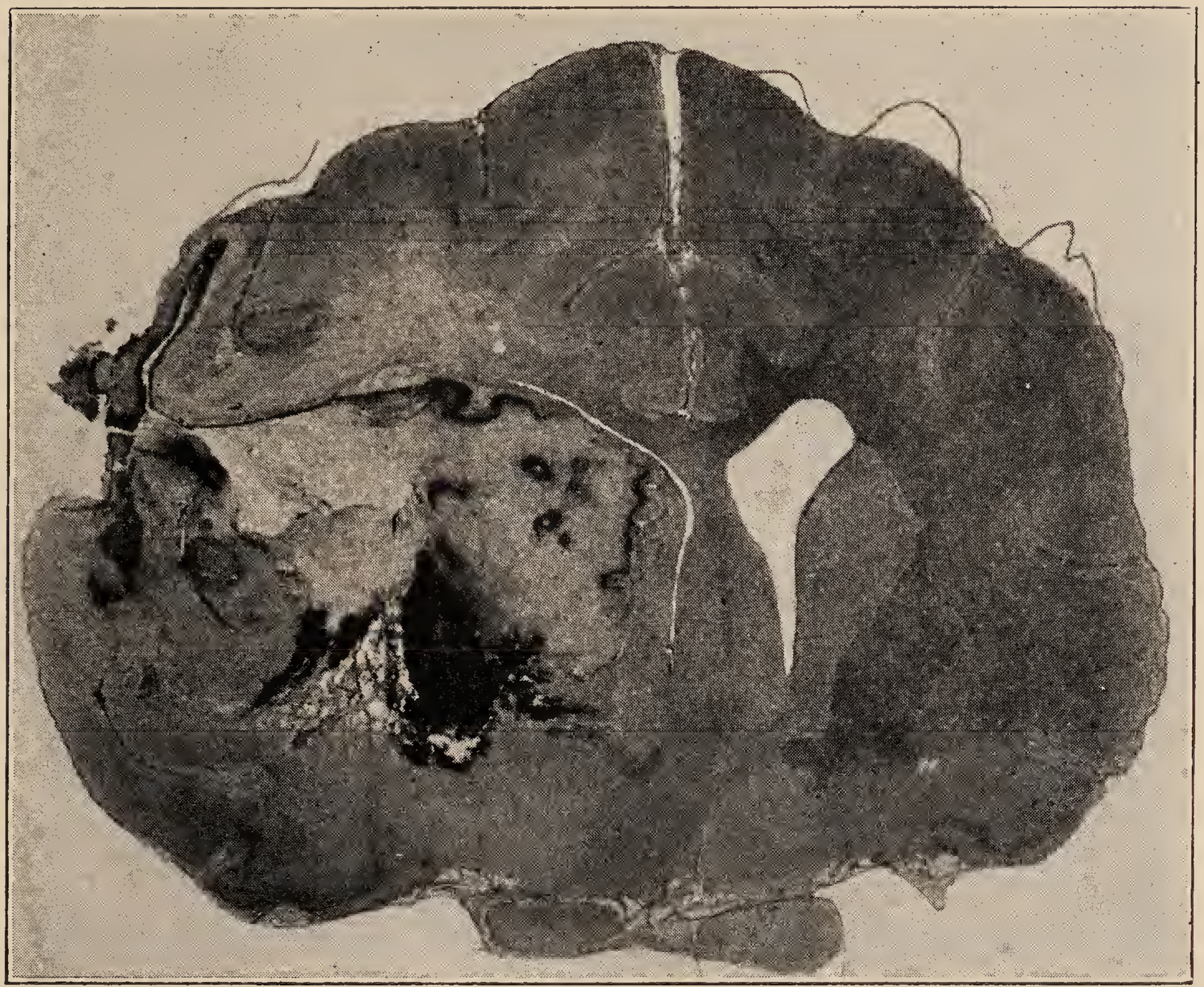

Fig. 16.

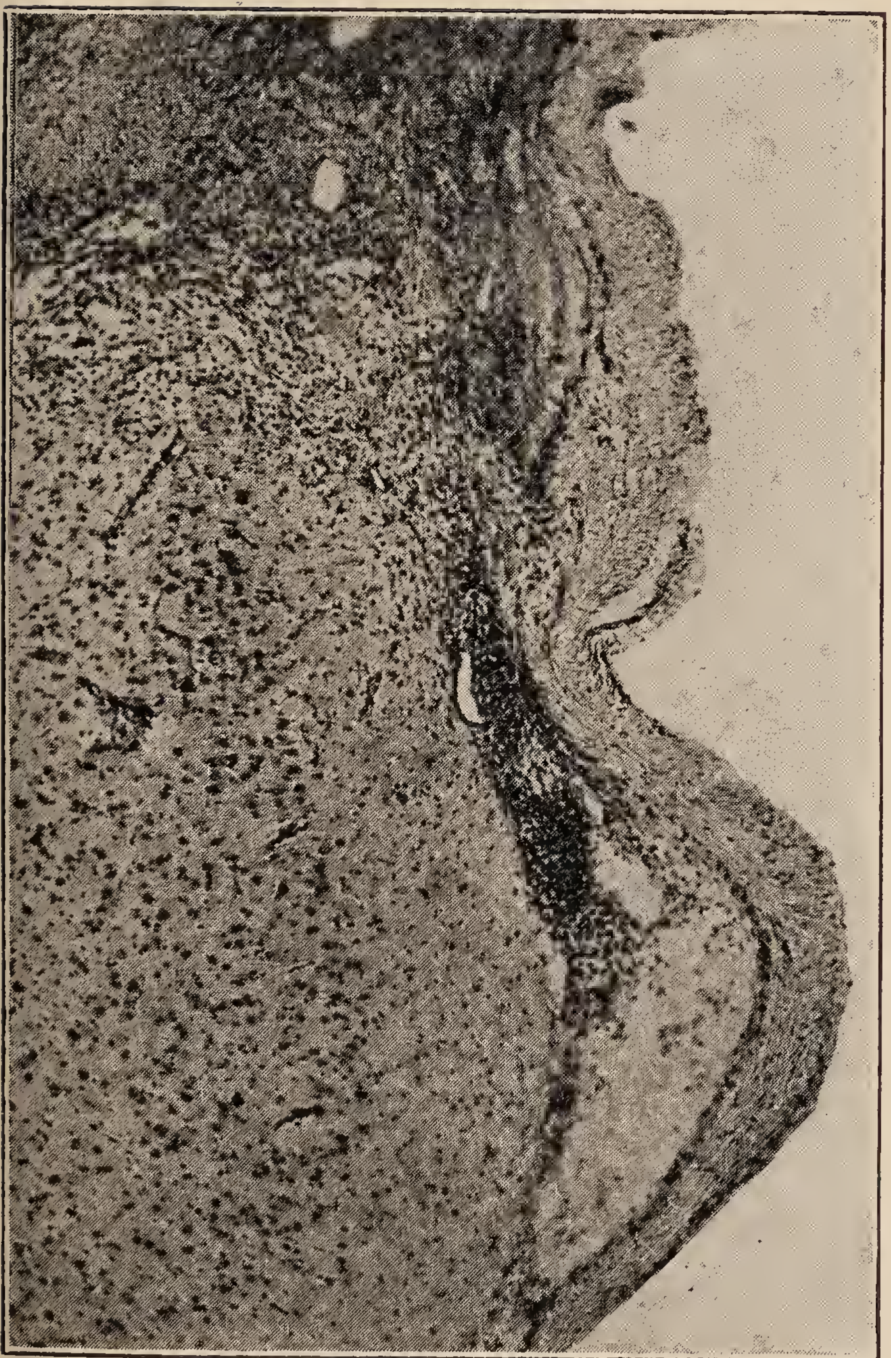

Fig. 17.

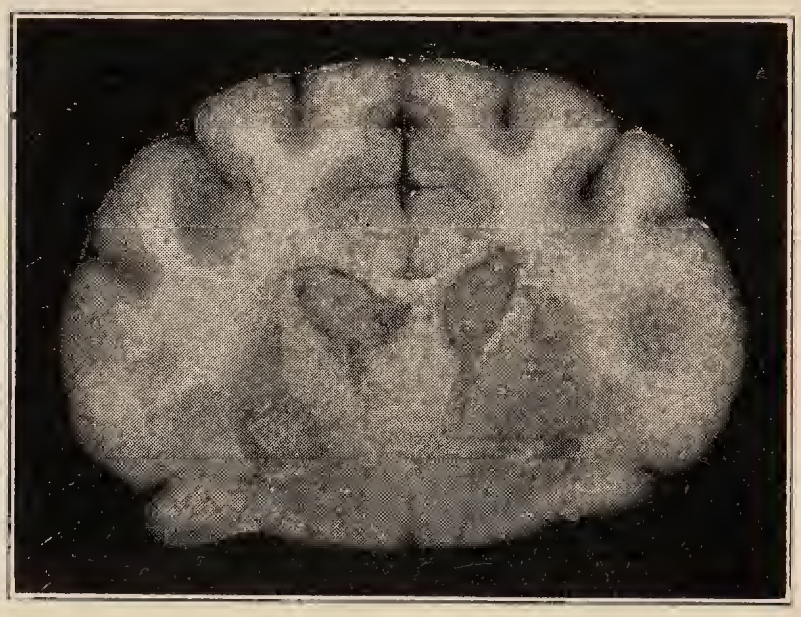

Fig. 18.

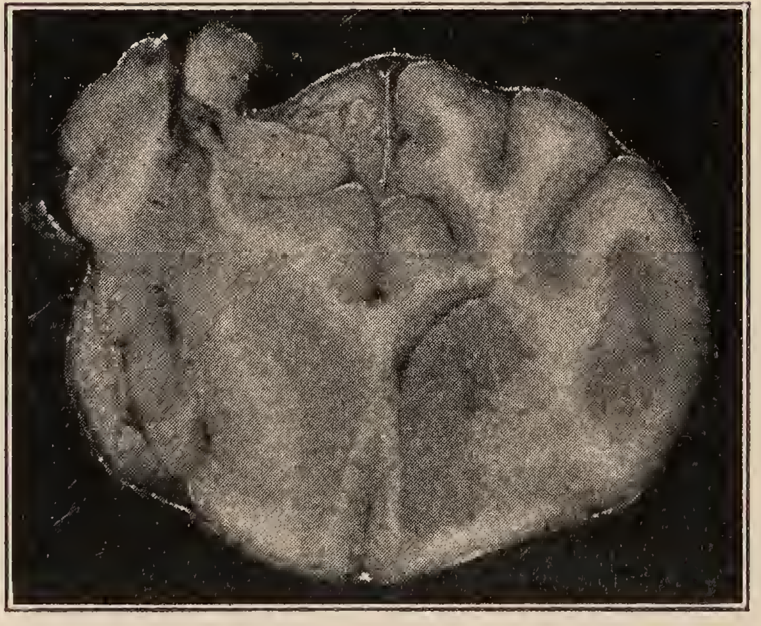

Fig. 19.